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Changing the natural history of type 2 diabetes: implications for clinical care
CONTROVERSIAL QUESTION

Do we focus enough on clinical outcomes when treating patients with type 2 diabetes?

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Achieving early and sustained glycemic control in type 2 diabetes – Bailey

Bailey

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The natural history of type 2 diabetes is typically a continuum of metabolic disruption associated with micro- and macrovascular complications. Diagnosis is usually preceded by years of gradual deterioration in the endocrine control of nutrient metabolism, giving rise to blood glucose concentrations that are above normal but below the threshold for diagnosis of diabetes. This prodromal state, characterized by impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG), is commonly referred to as prediabetes or intermediate hyperglycemia, and forms part of a collection of cardiovascular risk factors known as the metabolic syndrome.1-3 When blood glucose concentrations continue to rise, prediabetes progresses into type 2 diabetes, creating a highly variable and volatile mix of metabolic, vascular, and other chronic disturbances that pose a particularly difficult management challenge.

Etiology, pathogenesis, and prevalence

Most forms of type 2 diabetes emerge through the interaction of multiple genetic and environmental factors. Mutations of a small number of genes have been implicated in some cases, but altered expression levels of many genes appear to be involved in most cases. The impact of genetic factors is modulated by such environmental factors as the quality and quantity of the diet, physical exercise, comorbid conditions, and medications.4-6 Additionally, advancing age, male gender, greater parity and gestational diabetes in women, positive family history of adult-onset diabetes (which is probably a mix of genetic and behavioral influences), obesity, and certain ethnicities are known to accelerate the pathogenic process. The early endocrine defects responsible for impaired glucose homeostasis are insulin resistance (impaired insulin action) and a reduced and/or delayed initial (first phase) secretion of insulin in response to a prandial rise in blood glucose. During the emergence of intermediate hyperglycemia, the second phase of insulin secretion is usually accentuated. Excess adiposity, especially in visceral depots, promotes insulin resistance and escalates the hyperglycemia through an unmitting delivery of lipids to the liver and the production of adipokines that promote inflammation and counter insulin action.7,8

The currently accepted plasma glucose and glycated hemoglobin (HbA1c) values for prediabetes and for the diagnosis of diabetes are shown in Table I (page 4). The International Diabetes Federation (IDF) estimated that in 2013 the global prevalence of IGT was about 316 million compared with 382 million for diabetes (about 6.9% and 8.3% of the world population, respectively). These numbers are projected to rise to 471 million and 592 million for IGT and diabetes, respectively, by 2035.9
The extent to which hyperglycemia per se contributes to the increased risk of cardiovascular events in prediabetes (and diabetes) is keenly debated. Most people with prediabetes have additional cardiovascular risk factors that are components of the metabolic syndrome. Thus, visceral adiposity, raised blood pressure, various presentations of dyslipidemia (notably raised triglycerides and low levels of high-density lipoprotein cholesterol) are all features that accompany prediabetes and independently contribute to cardiovascular risk. The detrimental vascular effects of hyperglycemia are slowly generated compared with hypertension and dyslipidemia, and most people with prediabetes will exhibit insulin resistance (with or without hyperinsulinemia), which incurs a further independent cardiovascular risk. Insulin resistance reduces endothelial-dependent (nitric-oxide mediated) vasodilatation and reduces myocardial glucose metabolism. Insulin resistance with adiposity also promotes a prothrombotic state through altered production of adipoines, plasminogen-activated inhibitor-1, integrins and altered platelet function. Thus it is almost impossible to determine how much of the cardiovascular risk is attributable to each of the various concurrent risk factors.

The extent and duration of intermediate hyperglycemia in prediabetes is often dismissed as insufficient to generate significant microvascular risk, but several studies have identified increases in small vessel disease. For example, early stages of “diabetic” retinopathy have been observed in about 10% of patients with IGT and in up to 20% of people with advanced IFG. Impaired kidney function as indicated by an estimated glomerular filtration rate (eGFR)<60 mL/min per 1.73 m² and an albumin-creatinine ratio ≥30 mg/g is also encountered almost twice as frequently in prediabetes than in people with normal glucose tolerance. Features of early neuropathy are also evident in prediabetes.

Progression of prediabetes

Although the term prediabetes implies a prelude to type 2 diabetes, some people with prediabetes will revert to normal, usually through lifestyle adjustments of diet and exercise, and the extent to which hyperglycemia contributes to the increased risk of cardiovascular events in prediabetes (and diabetes) is keenly debated.

### Complications in prediabetes

Prediabetes carries an increased risk of cardiovascular disease, including cardiovascular death, nonfatal myocardial infarction and stroke, peripheral vascular disease, and heart failure. In the prospective DECODE study (Diabetes Epidemiology Collaborative analysis Of Diagnostic criteria in Europe) of 29 714 adults in 22 European cohorts, the risk of cardiovascular mortality was doubled by IGT and increased to a lesser extent by IFG. Other studies have reported similar findings although some have found that IFG is a stronger predictor of cardiovascular risk than IGT. Meta-analyses have suggested that the average increased risk of cardiovascular events, whether associated with IGT or IFG, or both, is about 20%. Many factors are anticipated to contribute to differences between studies, including the many factors that affect the pathogenesis of prediabetes listed in the preceding paragraph as well as the duration and severity of IGT, IFG, and HbA1c levels and the manner in which screening is undertaken. Each of these is likely to be measuring a different type of hyperglycemia affecting cardiovascular disease slightly differently, but in general it appears that the greater the exposure to intermediate hyperglycemia the greater the risk of cardiovascular events. Indeed, individuals with prediabetes are at increased risk of subclinical myocardial damage, as indicated by a raised cardiac troponin and abnormalities in their ECG.

### Table I. Definitions of intermediate hyperglycemia that constitute prediabetes, and diagnostic values for diabetes recommended by the American Diabetes Association.


#### Prediabetes

<table>
<thead>
<tr>
<th>Measure</th>
<th>Prediabetes</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fasting plasma glucose</strong></td>
<td>≥7.0 mmol/L</td>
<td>≥7.0 mmol/L</td>
</tr>
<tr>
<td>- impaired fasting glucose</td>
<td>≥126 mg/dL</td>
<td></td>
</tr>
<tr>
<td><strong>2-h OGTT plasma glucose</strong></td>
<td>≥11.1 mmol/L</td>
<td>≥200 mg/dL</td>
</tr>
<tr>
<td>- impaired glucose tolerance</td>
<td>≥120 mg/dL</td>
<td></td>
</tr>
<tr>
<td><strong>HbA1c</strong></td>
<td>≥5.7% to 6.4%</td>
<td>≥6.5%</td>
</tr>
<tr>
<td>- for prediabetes</td>
<td>39 to 47 mmol/mol</td>
<td>48 mmol/mol</td>
</tr>
</tbody>
</table>

**a** For diagnosis of diabetes based on fasting or random plasma glucose measurement, plasma glucose should be measured on two occasions, at least one of which is a laboratory measurement.

**b** Impaired fasting glucose is considered to be a fasting plasma glucose of 6.1 to <7.0 mmol/L (110 to 125 mg/dL) by WHO.

**c** 75-g Oral glucose tolerance test (OGTT) conducted after an overnight fast: plasma glucose values measured 2 h after consuming the glucose: usually a laboratory measurement.

**d** Value usually used for diagnosis of diabetes based on a random plasma glucose measurement.

**e** IFG (International Federation of Clinical Chemistry) (mmol/mol) or DCCT (Diabetes Control and Complications Trial) aligned (%) value.

**f** HbA1c for prediabetes considered to be 6.0%-6.4% (42-47 mmol/mol) by WHO.

**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD</td>
<td>Action to Control Cardiovascular Risk in Diabetes</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation</td>
</tr>
<tr>
<td>DECODE</td>
<td>Diabetes Epidemiology Collaborative analysis Of Diagnostic criteria in Europe</td>
</tr>
<tr>
<td>HbA1c</td>
<td>glycated hemoglobin</td>
</tr>
<tr>
<td>IDF</td>
<td>International Diabetes Federation</td>
</tr>
<tr>
<td>IFG</td>
<td>impaired fasting glucose</td>
</tr>
<tr>
<td>IGT</td>
<td>impaired glucose tolerance</td>
</tr>
<tr>
<td>UKPDS</td>
<td>United Kingdom Prospective Diabetes Study</td>
</tr>
<tr>
<td>VADT</td>
<td>Veterans Affairs Diabetes Trial</td>
</tr>
</tbody>
</table>
Achieving early and sustained glycemic control in type 2 diabetes – Bailey

Mandate for early effective glycemic control

Intensive glycemic control in the UKPDS with either a sulfonylurea or insulin reduced HbA1c by about 0.9% (10 mmol/mol) on average and deferred the onset and reduced the severity of the microvascular diseases. However, while there was a benefit for some macrovascular events, other major cardiovascular events such as myocardial infarction and stroke were not significantly affected. Metformin therapy in overweight patients did, however, reduce cardiovascular risk. This conundrum of glycemic control prompted initiation of other trials to examine the effect of intensive glycemic control on complications, but these were conducted in groups of much older patients starting several years after diagnosis. These trials were: ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation), and VADT (Veterans Affairs Diabetes Trial). They
confirmed the benefit of improved glycemic control to reduce the occurrence and severity of microvascular complications, as illustrated in several meta-analyses. However, like the UKPDS, they did not show a significant benefit against major cardiovascular disease and one of the trials (ACCORD) noted an increase in cardiovascular deaths.

At the same time, patients in the UKPDS entered a posttrial 8.5-year follow-up in which all participants received intensive glycemic control such that the HbA1c values became similar between groups for much of this period. Patients who had previously received intensive treatment now showed significantly lower cardiovascular event rates and reduced total mortality while maintaining their benefits of reduced microvascular disease. This indicated a “legacy effect” for both the macro- and microvascular events such that individuals receiving intensive glycemic control from the time of diagnosis gained lasting benefit. Considered in the context of ACCORD, ADVANCE, VADT and trials in prediabetes, it appears that improved glycemic control has consistently offered advantages within 1 to 5 years to slow the onset and/or reduce the severity of microvascular and neural complications, and the earlier in the disease process that intervention is made, the greater the gains.

The impact of improved glycemic control on macrovascular disease seems to take much longer; the UKPDS trial and posttrial follow-up covered a median period of 18.5 years from diagnosis, whereas ACCORD, ADVANCE, and VADT were each much shorter studies that started much later in the disease process and were probably not long enough to witness the full long-term effect on cardiovascular outcomes. Thus, the long-term benefits of early intensive control identified through the UKPDS and its posttrial follow-up strongly support the view that early, effective, and preferably sustained glycemic control can benefit macrovascular disease. Population-based observations of HbA1c and cardiovascular disease have also suggested that better glycemic control is associated with fewer cardiovascular events.

Comprehensive and individualised disease management

While prevention of type 2 diabetes and very early intervention to avoid protracted hyperglycemia offer benefits against microvascular and long-term macrovascular events, it is emphasized that a comprehensive therapeutic approach against a raft of cardiovascular risk factors is always recommended.

The Steno-2 study provided good evidence that control of blood pressure and dyslipidemia alongside glycemic control is very important, and that reductions in adiposity are invariably beneficial. Current guidelines are favoring an individualized patient-centered approach to the selection and timing of introduction of available therapies. Individualization is consistent with the heterogeneous presentation and progressive nature of type 2 diabetes, taking account of the variety and severity of complications. This diversity reflects the multivariable etiology and pathogenesis of type 2 diabetes, involving different mixtures of defects impacting to different extents. This in turn warrants the use of a range of different therapies at different times, often in combination, to address the many facets of the disease process. These include agents to address insulin resistance, enhance β-cell function, reduce excess glucagon, and assist weight reduction.

Conclusion

A protracted rise in blood glucose concentrations above normal, but below the diabetes threshold (prediabetes), is associated with increased cardiovascular risk. This is accentuated and accompanied by microvascular disease as the hyperglycemia escalates into type 2 diabetes. Early, effective control of blood glucose can defer the onset and reduce the severity of microvascular complications and can also reduce long-term cardiovascular risk. A wide range of therapeutic options is available to address hyperglycemia and cardiovascular risk, which could—and should—be used early and in a personalized manner to achieve effective disease management.

**Keywords:** cardiovascular risk, individualized therapy, metabolic syndrome, prediabetes, type 2 diabetes
The DECODE study group. Is the current definition for diabetes relevant to the Australian Diabetes, Obesity and Lifestyle (AusDiab) study. 2012;19:2297-2300.


Reaven G. The metabolic syndrome or the insulin resistance syndrome? Different names, different concepts, and different goals. EndocrinoMetab Clin North Am. 2004;33:293-303.


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L'histoire naturelle du diabète de type 2 se déroule généralement dans un continuum d’altérations métaboliques associées à des complications microvasculaires et macrovasculaires. Le diagnostic est généralement précédé par plusieurs années de détérioration progressive du contrôle endocrinien du métabolisme des nutriments, provoquant une augmentation des concentrations de glucose qui, pour être supérieures à la normale, ne dépassent pas le seuil diagnostique du diabète. Cet état prodromique, caractérisé par une tolérance au glucose altérée et/ou une glycémie à jeun altérée, est fréquemment désigné par le terme de prédiabète ou d’hyperglycémie intermédiaire, et fait partie de l’ensemble des facteurs de risque cardio-vasculaires qui composent le syndrome métabolique.1-3

Lorsque les concentrations sanguines de glucose continuent d’augmenter, le prédiabète progresse en diabète de type 2, créant un mélange « explosif » de différents troubles chroniques, notamment métaboliques et vasculaires, qui sont particulièrement difficiles à prendre en charge.

Étiologie, pathogénèse et prévalence
La plupart des formes de diabète de type 2 proviennent de l’interaction entre de multiples facteurs génétiques et environnementaux. Des mutations de quelques gènes ont été incriminées dans certains cas, mais l’altération des niveaux d’expression d’un grand nombre de gènes semble être à l’origine de la plupart d’entre eux.

L'impact des facteurs génétiques est modulé par différents facteurs environnementaux, notamment la qualité et la quantité de l’alimentation, l’exercice physique, les comorbidités et les traitements médicamenteux.4-6 En outre, un âge avancé, le sexe masculin, un nombre élevé de grossesses et un diabète gestationnel chez la femme, des antécédents familiaux de diabète tardif (qui résultent probablement d’un mélange d’influences génétiques et comportementales), l’obésité et certaines origines ethniques peuvent accélérer le processus pathogène.

Les valeurs actuellement acceptées de la glycémie et de l’hémoglobine glyquée (HbA1c) pour le prédiabète et le diagnostic du diabète sont présentées dans le Tableau 1. La Fédération internationale du diabète (International Diabetes Federation, IDF) a estimé qu’en 2013 la prévalence globale de l’altération de la tolérance au glucose avait été d’environ 316 millions par rapport à 297 millions pour le diabète (respectivement 6,9 % et 8,3 % de la population mondiale). Ces chiffres devraient augmenter respectivement jusqu’à 471 millions et 592 millions en 2035.3

Complications dans le prédiabète

Le prédiabète est associé à un risque accru de maladies cardio-vasculaires, notamment de mortalité cardio-vasculaire, d’infarctus du myocarde non fatal et d’accident vasculaire cérébral non fatal, de vasculopathie périphérique et d’insuffisance cardiaque. Dans l’étude prospective DECODE (Diabetes Epidemic Collaborative analysis Of Diagnostic criteria in Europe, Épidémiologie du diabète, Analyse collaboratrice des critères diagnostiques en Europe) menée chez 29 714 adultes dans 22 cohortes européennes, le risque de mortalité cardio-vasculaire a été doublé en cas d’altération de la tolérance au glucose et augmenté dans une moindre mesure en cas d’altération de la glycémie à jeun.13 D’autres études ont rapporté des résultats similaires, bien que certaines aient conclu qu’une altération de la glycémie à jeun est un facteur prédicatif plus puissant du risque cardio-vasculaire qu’une l’altération de la tolérance au glucose.14-15 Des méta-analyses ont suggéré que l’augmentation moyenne du risque d’événements cardio-vasculaires, associée à une tolérance altérée au glucose ou à une glycémie à jeun altérée, ou aux deux, était d’environ 20 %.14,15 De nombreux facteurs pourraient contribuer à créer des différences entre les études, notamment les nombreux facteurs affectant la pathogenèse du prédiabète indiqués dans le paragraphe précédent, ainsi que la durée et la sévérité de l’altération de la tolérance au glucose, de l’altération de la glycémie à jeun, des valeurs de l’HbA1c, et la manière dont la sélection est réalisée. Chacun de ces facteurs devrait mesurer un type différent d’hyperglycémie affectant de manière légèrement différente les maladies cardio-vasculaires, mais il apparaît en général que plus l’exposition à une hyperglycémie intermédiaire est importante, plus le risque d’événements cardio-vasculaires est élevé. En effet, les personnes présentant un prédiabète sont exposées à un risque majoré de lésions myocardiques subcliniques, comme l’indique l’augmentation de la troponine cardiaque et les anomalies de l’ECG.16

La question du niveau de contribution de l’hyperglycémie à l’augmentation du risque d’événements cardio-vasculaires dans le prédiabète (et le diabète) fait l’objet d’apres débats.18 La plupart des personnes prédiabétiques présentent des fac-
Au fur et à mesure que le prédiabète progresse en diabète de type 2, l'insulinorésistance peut devenir légèrement plus sévère, mais il existe une détérioration notable de la fonction des cellules β, avec une perte de la première phase de la sécrétion d'insuline induite par le glucose et une deuxième phase fortement réduites. Les cellules β sécrètent une proportion plus élevée de pro-insuline (beaucoup moins active que l'insuline) et perdent le schéma rythmique normal de la sécrétion d'insuline — autant d'éléments démontrant l'émergence d'une insuffisance des cellules β. Les principaux moteurs contribuant à l'aggravation de l'hyperglycémie sont une insuffisance sévère des cellules β ainsi que d'autres facteurs endocriniens favorisants, notamment une sécrétion excessive de glucagon et une altération de la capacité des hormones intestinales à favoriser la sécrétion d'insuline induite par les nutriments (altération de l'effet incrétine).

Complications lors du diagnostic du diabète de type 2

Lors du diagnostic d'un diabète de type 2, il n'est pas inhabituel de mesurer une valeur d'HbA1c d'environ 9 % (75 mmol/mol). La plupart des patients diabétiques de type 2 ont probablement cette affection depuis plusieurs années avant qu'elle ne soit diagnostiquée, et chez environ un quart des patients les complications ont d'ores et déjà eu le temps de se développer. L'IDF a estimé que près de 175 millions de personnes à travers le monde pourraient ne pas avoir connais-
sance de leur diabète, et qu'environ 1 % des adultes des pays occidentaux sont probablement atteint d'un diabète non diagnostiqué. Par extrapolation rétrospective des chiffres de l'aug-
méntation annuelle moyenne des complications microvascu-
laires après le diagnostic du diabète, il semble que le patient moyen pourrait avoir été exposé à un certain degré d'hyper-
glycémie depuis environ 10 ans. L'extrapolation rétrospec-
tive des données de l'étude UKPDS (United Kingdom Pros-
pective Diabetes Study, Étude prospective sur le diabète du Royaume-Uni) a donné une estimation similaire de l'expo-
sition antérieure à une hyperglycémie et d'autres estimations ont indiqué une durée de 4 à 7 ans. Ces estimations concor-
dent avec un taux de progression moyen du prédiabète en diabète manifeste d'environ 5 % à 7 % par an.

Lorsque la valeur de la glycémie n'a que faiblement augmenté (par exemple glycémie quotidienne moyenne inférieure à 10 mmol/L), la plus grande partie de l'exposition supplémentaire au glucose est vraisemblablement postprandiale; de même,
il existe souvent d’importantes fluctuations de la glycémie (dénommées labilité glycémique). Ces deux caractéristiques du profil hyperglycémique sont considérées comme particulièrement néfastes pour l’endothélium. Par conséquent, il est probable que les complications macrovasculaires, mais également microvasculaires soient déjà avancées chez certaines personnes lors du diagnostic. Dans l’étude UKPDS (âge médian lors du diagnostic de 53 ans avec une HbA1c, environ 9 % [75 mmol/mol] avant les mesures diététiques et la randomisation), les prévalences des complications observées lors du diagnostic étaient les suivantes : rétinopathie 21 % (> 1 microanévrisme), anomalie de l’ECG 18 %, absence de sens de la vibration 7 %, angor 3 %, claudication intermittente 3 %, infarctus du myocarde 2 % et accident vasculaire cérébral ou accident ischémique transitoire 1 %. Les prévalences d’autres caractéristiques cliniques étaient les suivantes : hypertension 25 %, microalbuminurie 18 %, protéinurie 2 % et dysfonction érectile 20 %. Plus de 75 % des patients présentaient un surpoids ou une obésité lors du diagnostic, et certains présentaient une dyslipidémie. Bien que les procédures de sélection et les critères diagnostiques aient varié entre les études, il apparaît que les patients atteints de diabète de type 2 présentent toujours un grand nombre de complications lors du diagnostic, ce qui signifie qu’elles étaient atténuées de diabète depuis plusieurs années avant que cette affection ne soit identifiée.

Progression des complications
L’histoire naturelle du diabète de type 2 est un déclin continu du contrôle métabolique qui entraîne une accumulation de complications. L’étude UKPDS apporte des informations sur l’évolution chronologique de ce processus chez les patients recevant une intervention conventionnelle (principalement diététique) à partir du moment du diagnostic : l’HbA1c, a été initialement réduite d’environ 9,0 % à environ 7,0 % (53-75 mmol/mol) par des mesures diététiques concertées, puis a augmenté progressivement d’environ 7,0 % (53 mmol/mol) à plus de 8,5 % (70 mmol/mol) en 15 ans. Pendant cette période, la morbidité et la mortalité ont été fortement augmentées par rapport à la population générale. En 10 ans, le risque absolu de complications (pour 1 000 années-patients) a été le suivant : 18,9 pour la mortalité de toute cause, 11,5 pour la mortalité liée au diabète, 17,4 pour l’infarctus du myocarde, 5,0 pour l’accident vasculaire cérébral, 1,6 pour l’amputation, 3,3 pour l’insuffisance cardiaque, 0,8 pour l’insuffisance rénale, 11,0 pour la photocoagulation rétinienne et 4,4 pour la mortalité liée au cancer.

Nécessité d’un contrôle glycémique efficace précoce
Un contrôle glycémique intensif dans l’étude UKPDS par un sulfonylure hypoglycémiant ou l’insuline a réduit l’HbA1c, d’environ 0,9 % (10 mmol/mol) en moyenne et a retardé le déclenchement et réduit la sévérité des maladies microvasculaires. Cependant, si un bénéfice pour certains événements macrovasculaires a été observé, les autres événements cardio-vasculaires majeurs, notamment les infarctus du myocarde et les accidents vasculaire cérébraux, n’ont pas été affectés de manière significative. Un traitement par la metformine chez les patients en surpoids a cependant réduit le risque cardio-vasculaire. Cette énigme du contrôle glycémique a motivé la mise en Œuvre d’autres études destinées à examiner l’effet d’un contrôle glycémique intensif sur les complications, mais celles-ci ont été réalisées chez des groupes de patients beaucoup plus âgés et ont commencé plusieurs années après le diagnostic. Ces études ont été les suivantes : Action to Control CardioVascular Risk in Diabetes (Action pour le contrôle du risque cardio-vasculaire dans le diabète, ACCORD), Action in Diabetes and Vascular disease : Prévention de la Mortalité et des Maladies Vasculaires (ÉTUDE ACCORD), Action in Diabetes and Vascular disease : Prévention et Traitement de l’Insuffisance rénale (ÉTUDE ADVANCE), et Veterans Affairs Diabetes Trial (ÉTUDE sur le diabète chez les anciens combattants, VADT). Elles ont confirmé le bénéfice d’un meilleur contrôle glycémique pour réduire la survenue et la sévérité des complications microvasculaires, comme l’ont montré plusieurs méta-analyses Cependant, comme dans l’étude UKPDS, elles n’ont pas mis en évidence de bénéfices significatifs contre les maladies cardio-vasculaires majeures, et l’une de ces études (ACCORD) a même observé une augmentation de la mortalité cardio-vasculaire.

Parallèlement, les patients de l’étude UKPDS ont commencé un suivi post-étude de 8,5 ans au cours duquel tous les participants ont bénéficié d’un contrôle glycémique intensif, de telle sorte que les valeurs de l’HbA1c sont devenues similaires entre les groupes pendant une grande partie de cette période. Les patients ayant précédemment reçu un traitement intensif montraient désormais des taux d’événements cardio-vasculaires significativement inférieurs et une réduction de la mortalité totale, tout en continuant à bénéficier d’une réduction des maladies microvasculaires. Cela indique un effet pérenne (+ legacy effect +) en ce qui concerne les événements macrovasculaires et microvasculaires, de telle sorte que les personnes bénéficiant d’un contrôle glycémique intensif à partir du diagnostic recueillent un bénéfice durable. Dans le cadre des études ACCORD, ADVANCE, VADT et d’autres études sur le prédiaabète, il est apparu qu’un meilleur contrôle glycémique entraînait des avantages dans les 1 à 5 ans aboutissant à une diminution du déclenchement et/ou une réduction de la sévérité des complications microvasculaires et neurales, montrant que plus l’intervention était effectuée précoce au cours du processus pathologique, plus les gains étaient importants.

L’impact de l’amélioration du contrôle glycémique sur les maladies macrovasculaires semble prendre davantage de temps : l’étude UKPDS et le suivi post-étude ont couvert une période médiane de 18,5 ans à partir du diagnostic, tandis que les
études ACCORD, ADVANCE et VADT ont été chacune beaucoup plus courtes, elles ont commencé beaucoup plus tardivement au cours du processus pathologique et n’ont probablement pas été assez longues pour mettre en évidence le plein effet à long terme sur les résultats cardio-vasculaires. Par conséquent, les bénéfices à long terme d’un contrôle intensif précoce observé pendant l’étude UKPDS et son suivi post-étude confirment de manière manifeste le fait qu’un contrôle glycémique efficace et – de préférence – prolongé entraîne des bénéfices sur les maladies macrovasculaires. Les observations basées sur la population relatives à l’HbA1c et aux maladies cardio-vasculaires ont également suggéré qu’un meilleur contrôle glycémique était associé à une diminution des événements cardio-vasculaires.60

Prise en charge complète et individualisée de la maladie
Si la prévention du diabète de type 2 et une intervention très précoce visant à éviter une hyperglycémie prolongée apportent des bénéfices contre les événements microvasculaires et macrovasculaires à long terme, il faut souligner qu’une approche thérapeutique complète contre un grand nombre de facteurs de risque cardio-vasculaire est toujours recommandée. L’étude Steno-2 a apporté des preuves convaincantes de l’importance d’associer un contrôle de la pression artérielle et de la dyslipidémie à un contrôle glycémique,61,62 et a montré qu’une réduction de l’adiposité est invariablement bénéfique.63


Conclusion
Une augmentation prolongée des concentrations sanguines de glucose au-delà des valeurs normales, mais inférieure au seuil diabétique (prédiabète), est associée à une aggravation du risque cardio-vasculaire. Ce phénomène est accentué et accompagné de maladies microvasculaires, lorsque l’hyperglycémie évolue en diabète type 2. Un contrôle glycémique précoce et efficace peut retarder la survenue et réduire la sévérité des complications microvasculaires, mais également réduire le risque cardio-vasculaire à long terme. Un grand nombre d’options thérapeutiques disponibles pour traiter l’hyperglycémie et le risque cardio-vasculaire pourraient – et devraient – être utilisées précoce et de manière personnalisée afin de permettre une prise en charge efficace de la maladie.

Keywords: risque cardio-vasculaire, traitement individualisé, syndrome métabolique, prédiabète, diabète de type 2
Achieving “optimal” glycemic control: individualization of target

by S. Colagiuri, Australia

Although improved glycemic control has been shown to prevent or reduce complications in patients with type 2 diabetes, intensive glycemic control may not benefit every patient, and may in some cases be harmful. In particular, the occurrence of serious hypoglycemia is of concern, especially since it may increase the risk of adverse cardiovascular outcomes. Setting glycemic targets therefore requires careful balancing of potential benefits and harms, and should take into account an individual’s phenotypic characteristics. Consequently, a patient-centered approach to the medical management of diabetes is now increasingly emphasized in diabetes management guidelines, and the HbA1c target of 7.0% suggested by most guidelines should be considered as a starting point from which to set patient-specific targets according to individual patient factors. The main factors that are usually considered include age, hypoglycemia risk, diabetes duration, complications, comorbidities, and impaired renal function. Patient preferences are also important, and the target should be agreed between patient and health professional. HbA1c targets will also be influenced by previous attempts to optimize glycemic control: a lower target may be set if it can be easily and safely achieved, and conversely, a higher target should be considered when previous attempts to optimize glycemic control have been associated with unacceptable adverse effects. Once set, the chosen HbA1c target should be reviewed regularly, taking into account benefits, safety, and tolerability, and adjusted when clinical circumstances change.

Medicographia. 2016;38:14-19 (see French abstract on page 14)
Changing the Natural History of Type 2 Diabetes: Implications for Clinical Care

Achieving “optimal” glycemic control: individualization of target – Colagiuri

Table I. Outcome studies with prespecified HbA1c targets.

<table>
<thead>
<tr>
<th>Study</th>
<th>Target HbA1c</th>
<th>Achieved HbA1c</th>
<th>Specific intensive therapy</th>
<th>Outcomes of intensive therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD6</td>
<td>Intensive: &lt;6.0% Standard: 7.0%-7.9%</td>
<td>Intensive: 6.4% Standard: 7.5%</td>
<td>Nil</td>
<td>Primary outcome not different Increased all-cause mortality</td>
</tr>
<tr>
<td>Advance6</td>
<td>Intensive: ≤6.5% Standard: 7.0%-7.9%</td>
<td>Intensive: 6.5% Standard: 7.5%</td>
<td>Gliclazide MR</td>
<td>Reduced renal events</td>
</tr>
<tr>
<td>VADT7</td>
<td>Intensive: 4.8%-6.0% Standard: 8.0%-9.0%</td>
<td>Intensive: 6.9% Standard: 8.4%</td>
<td>Nil</td>
<td>Reduced albuminuria</td>
</tr>
</tbody>
</table>

Table II. Outcome studies comparing intensive and conventional therapy without prespecified HbA1c targets.

<table>
<thead>
<tr>
<th>Study</th>
<th>Target</th>
<th>Achieved HbA1c</th>
<th>Specific intensive therapy</th>
<th>Outcomes of intensive therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT1</td>
<td>Intensive: 6.05% Standard: no symptoms, normal growth, no hypoglycemia</td>
<td>Intensive: 7.2% Standard: 9.0%</td>
<td>MDI or insulin pump</td>
<td>Reduced microvascular events</td>
</tr>
<tr>
<td>Kumamoto8</td>
<td>Intensive: near normal blood glucose and HbA1c approx. 7.0% Standard: no symptoms of hyper or hypoglycemia</td>
<td>Intensive: 7.1% Standard: 9.4%</td>
<td>MDI</td>
<td>Reduced microvascular events</td>
</tr>
<tr>
<td>UKPDS2</td>
<td>Intensive: fasting blood glucose &lt;6.0 mmol/l Standard: medications added if symptoms of hyperglycemia or fasting blood glucose &gt;15 mmol/l</td>
<td>Intensive: 7.0% Standard: 7.9%</td>
<td>Various</td>
<td>Reduced microvascular events</td>
</tr>
</tbody>
</table>

Sess of randomized controlled trials (RCTs). Tables I and II summarize the major RCTs that have examined the effects of intensive glycemic control, with or without prespecified HbA1c targets. The majority of studies reported microvascular benefits with an achieved HbA1c of around 7.0%, while the ACCORD study (Action to Control Cardiovascular Risk in Diabetes) reported adverse mortality outcomes with an achieved HbA1c in the intensive group of 6.4%. All studies reported an increase risk of hypoglycemia with lower HbA1c levels.

Most guidelines recommend an HbA1c target below 7.0% measured by a DCCT (Diabetes Control and Complications Trial)-aligned assay in order to minimize the risk of developing diabetes-related complications and minimize the risk of adverse events, especially hypoglycemia.

Individualizing targets

A general HbA1c target is useful for assessing quality of care at a population level. At an individual level it is also useful as a starting point for individualizing a treatment goal and guiding and changing interventions if the target is not attained. Setting and adjusting HbA1c treatment targets should balance potential benefits and possible harms, and a number of publications have suggested ways in which targets can be personalized.

Personalizing an HbA1c target is based on an individual’s phenotypic characteristics. The main factors that are usually considered include age, hypoglycemia risk, diabetes duration, complications, comorbidities, and renal function. In addition, there are a number of relevant practical considerations.

Patient preferences are important, and the target should be agreed between patient and health professional. HbA1c targets will also be influenced by experience of previous attempts to optimize glucemic control: a lower target may be considered if it is easily and safely achieved, and conversely, a higher target should be considered when previous attempts to optimize control have been associated with unacceptable consequences. The target should be regularly reviewed taking into account benefits, safety, and tolerability, and adjusted according to the clinical course of the individual.
Considerations in individualizing HbA1c treatment targets.

- **Age**
  Age is an important consideration with younger people having a greater potential than older people to benefit from lower HbA1c targets, which is related primarily to longer life expectancy and the potential harm of a longer exposure to hyperglycemia.

- **HbA1c targets**
  HbA1c targets frequently require modifying in older people with diabetes. The International Diabetes Federation (IDF) guidance for the management of older people with diabetes is based not on age per se but on functional categorization of older people with diabetes, taking into consideration comorbidities and functional status. Significant for diabetes and setting HbA1c targets is an increased vulnerability to hypoglycemia, diminishing life expectancy, and cognitive dysfunction and frailty.13

The IDF guidelines describe three main categories for older individuals with diabetes as a basis for clinical decision-making, including setting glycemic targets and treatment intensification (Table III).

- **Category 1: Functionally independent**
  This category includes people who are living independently, have no important impairments of activities of daily living (ADL), and who are receiving none or minimal caregiver support. The usual HbA1c target is 7.0%–7.5% and the full range of therapeutic options can be considered in this category.

- **Category 2: Functionally dependent**
  This category includes individuals who, due to loss of function, have impairments of ADLs such as bathing, dressing, or personal care and are at particular risk of requiring admission to a care (nursing) home. The usual HbA1c target is 7.0%–8.0%. There should be an emphasis on choosing medications with a low potential for hypoglycemia and simplified insulin regimens with a low hypoglycemic risk.

- **Category 3: End of life care**
  This category includes individuals with a significant medical illness or malignancy and whose life expectancy has been reduced to less than 1 year. The glycemic target is to avoid symptomatic hyperglycemia, minimize the risk of hypoglycemia, and consider appropriate withdrawal of therapy, including insulin, during the terminal stage.

### Table III. General glycemic targets according to functional category

<table>
<thead>
<tr>
<th>Functional category</th>
<th>General HbA1c target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functionally independent</td>
<td>7.0%-7.5%</td>
</tr>
<tr>
<td>Functionally dependent</td>
<td>7.0%-8.0%</td>
</tr>
<tr>
<td>Frail</td>
<td>Up to 8.5%</td>
</tr>
<tr>
<td>Dementia</td>
<td>Up to 8.5%</td>
</tr>
<tr>
<td>End of life</td>
<td>Avoid symptomatic hyperglycemia</td>
</tr>
</tbody>
</table>

This category includes two particular subgroups requiring special consideration:

- **Frailty**, which is characterized by a combination of significant fatigue, recent weight loss, severe restriction in mobility and strength, increased propensity to falls, and increased risk of institutionalization. Frailty affects up to 25% of older people with diabetes. An HbA1c target up to 8.5% may be appropriate. Medications that might cause nausea or gastrointestinal disturbance or excess weight loss (eg, metformin, glucagon-like peptide-1 [GLP-1] receptor agonists, sodium-glucose transport protein 2 [SGLT2] inhibitors) should be avoided or discontinued.

- **Dementia**, which is characterized by cognitive impairment with significant memory problems, a degree of disorientation or a change in personality, and an inability to self-care. Many will be relatively physically well. An HbA1c target up to 8.5% may be appropriate and caregivers and/or family should be educated to recognize the subtle indicators of hypoglycemia. The emphasis of treatment is on patient safety, avoiding hypoglycemia and unacceptable hyperglycemia, using simplified regimens and providing family/patient education and support.

### Hypoglycemia

Occurrence of or potential risk of severe hypoglycemia is a major consideration in setting glycemic targets. Hypoglycemia is the most common adverse effect of blood glucose-lowering therapy and its occurrence is influenced by treatment modality and complexity, factors which affect metabolism of the medication, particularly renal impairment,14,15 and patient factors including adherence to treatment regimen, mental function, and hypoglycemia awareness.16 Severe hypoglycemia impacts the quality of life, increases the risk of falls and...
injuries, and may increase the risk of adverse cardiovascular outcomes. The ADVANCE study (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation) reported an association between severe hypoglycemia and increased risk of cardiovascular death. However, the annual death rate was actually lower in the group receiving intensive treatment (3.6% vs 5.1%). Despite the higher rate of severe hypoglycemia, intensive glucose control was not associated with excess mortality. While the reason for the increased all-cause mortality in the ACCORD study remains unexplained, intensive treatment tripled the frequency of severe hypoglycemia and speculation continues that this may have contributed to the increased mortality. Simultaneous 24-h ECG and continuous glucose monitoring have reported an association between nocturnal hypoglycemia and prolonged corrected QT interval, and disturbing changes in cardiac rate and rhythm.

People who experience recurrent severe hypoglycemia or in whom there is a high risk associated with possible severe hypoglycemia (eg, with certain occupations or the elderly who live alone), should have their HbA1c target increased by about 0.5%.

**Duration of diabetes**

Interventions in the earlier stages of type 2 diabetes are generally considered to be associated with better outcomes, but the evidence is limited. This has been interpreted to support setting lower HbA1c targets with shorter diabetes duration. The UKPDS (United Kingdom Prospective Diabetes Study) is the only outcome study in people with newly diagnosed diabetes and showed benefits on microvascular outcomes of more intensive control compared with conventional treatment. With longer-term follow up, benefits emerged in relation to risk reductions in myocardial infarction and death from any cause. The evidence in relation to the long-term effects of intensive glycemic control in people with type 2 diabetes with longer diabetes duration has been mixed. The ADVANCE-ON study of subjects with diabetes duration of 8 years at the time of recruitment did not find emerging benefits of more intensive vs conventional treatment. The VADT study (Veterans Affairs Diabetes Trial) in people with type 2 diabetes duration of 11.5 years at recruitment, recently reported emerging long-term benefits of intensive glycemic control in time to the first major cardiovascular event. In addition to potential outcome benefits, more aggressive treatment in people with shorter duration of diabetes may be associated with less potential harm from hypoglycemia.

**Diabetes complications**

The presence of complications is another consideration when setting HbA1c targets. All studies of intensive blood glucose-lowering interventions have shown that lower HbA1c levels reduce the development or progression of microvascular complications. Therefore, people with no or early signs of microvascular complications could potentially benefit from tighter control, provided there are no other modifying considerations. There is limited evidence of the benefits of tight glycemic control per se on macrovascular disease in the short term, but there is accumulating evidence that benefits may accrue in the longer term. Multifactorial treatment including more intensive glycemic control has been shown to be beneficial both in the short and longer term in reducing premature mortality and a range of macrovascular and microvascular outcomes.

A group of particular interest is people with diabetes with established cardiovascular disease, a common occurrence in type 2 diabetes. There is no convincing evidence that tight glycemic control has particular benefits in this group as evidenced from a number of outcome studies including ACCORD, ADVANCE, and ORIGIN (Outcome Reduction with an Initial Glargine Intervention). As noted in the hypoglycemia section, caution is warranted in setting low HbA1c targets in people with established cardiovascular disease because of the potential risk associated with the occurrence of severe hypoglycemia related to the increased risk of adverse outcomes and predisposition to induce arrhythmias. Consequently, the presence of established cardiovascular disease warrants a more cautious approach and adopting a less stringent HbA1c target.

**Comorbidities**

Comorbidities are common in people with type 2 diabetes, especially with increasing age and diabetes duration. Concomitant treatment of significant comorbidities increases the number of medications and the overall burden of disease, and increases the risks associated with complex management regimens, including poor adherence due to errors, confusion, and side effects. Higher HbA1c targets should be considered in these patients.

**Impaired renal function**

Renal insufficiency is an important consideration in choosing blood glucose-lowering therapy due to the potential effect of impaired renal function in altering drug metabolism. This may result in an increase in the medication’s blood glucose-lowering effect, thereby increasing the risk of hypoglycemia (eg, certain sulfonylureas), or it may diminish its efficacy (eg, SGLT2 inhibitors), or may result in the accumulation of potentially harmful metabolites (eg, metformin).

In addition, in patients with diabetes and chronic kidney disease, HbA1c may not accurately reflect glycemic control. Factors which may contribute to this effect include increased levels of urea directly interacting with HbA1c assays, reduced erythropoiesis, shortened red blood cell half-life, the use of iron and erythropoiesis stimulating agents (ESAs), and blood transfusions. A recent study reported that in people with type 2 diabetes and chronic kidney disease, the usual linear rela-
tionship observed between HbA1c and average glucose is attenuated by use of ESAs and results in a systematic underestimation of the average glucose level derived from HbA1c.25

Consequently, there are a number of competing considerations when setting HbA1c targets in people with type 2 diabetes and renal insufficiency. It is therefore important when setting and reviewing HbA1c targets to monitor renal function closely—especially in older people—by measuring creatinine and calculating the estimated glomerular filtration rate (eGFR).

Conclusion

Glycemic control is closely related to diabetes-specific complications, and more intensive glycemic control has been shown unequivocally to prevent or reduce these complications. However, overly aggressive blood glucose-lowering can be associated with harms, particularly the occurrence of serious hypoglycemia. Consequently, setting glycemic targets requires careful balancing of potential benefits and harms. Although most guidelines suggest a general HbA1c target of 7.0%, this should be considered only as a starting point from which individual patient factors should be taken into consideration in setting a specific target for an individual. There are several factors that influence an individual's risk-to-benefit ratio and which need to be considered, including age, duration of diabetes, risk of hypoglycemia, and presence of complications, comorbidities, and impaired renal function. Once set, the appropriateness of the chosen HbA1c target should be frequently reviewed and modified if necessary, especially when individual patient circumstances change.

References

Améliorer le contrôle glycémique prévient ou diminue les complications chez les diabétiques de type 2, mais un contrôle glycémique intensif ne convient pas à tous les patients et peut même dans certains cas être délétère. La survenue d’hypoglycémies sévères est notamment préoccupante parce qu’elle peut augmenter le risque d’événements cardio-vasculaires indésirables. Fixer des cibles glycémiques nécessite donc d’évaluer soigneusement les avantages et les inconvénients potentiels et de prendre en compte les caractéristiques phénotypiques individuelles des patients. De fait, les recommandations actuelles de prise en charge du diabète mettent de plus en plus l’accent sur une approche médicale du diabète centrée sur le patient. Le taux ciblé d’HbA1c de 7 % préconisé par la plupart des recommandations doit être considéré comme un point de départ à partir duquel des valeurs spécifiques à chaque patient sont choisies, selon ses facteurs individuels. Les principaux facteurs habituellement pris en compte sont : l’âge, le risque hypoglycémique, la durée du diabète, la présence de complications et de comorbidités, et une fonction rénale altérée. Les préférences des patients sont également importantes et le patient et le professionnel de santé doivent s’accorder sur le taux ciblé. Les tentatives antérieures d’optimisation du contrôle glycémique influent aussi sur la détermination de l’HbA1c ciblée : une valeur plus basse peut être envisagée si elle peut être facilement atteinte et en toute sécurité alors qu’une valeur plus haute doit être préférée en cas d’effets indésirables inacceptables lors de tentatives antérieures du contrôle glycémique. Une fois choisi, le taux ciblé d’HbA1c doit être réévalué régulièrement en considérant les bénéfices, la sécurité d’emploi, la tolérance et doit être ajusté en fonction des circonstances cliniques.
Diabetes care historically has prioritized glycemic control over other metabolic and pathophysiological factors as the main method by which diabetes-related morbidity and mortality can be reduced. The hallmark of diabetes mellitus is an elevation of the blood glucose and it was presumed that if blood glucose was near normalized it would follow that associated co-morbidities could be potentially avoided or markedly improved. The landmark trial in type 2 diabetes, UKPDS (United Kingdom Prospective Diabetes Study), did not, however, fully support this, and although it demonstrated significant benefits of glycemic control in reducing microvascular complications, the same magnitude of benefits was not initially seen in macrovascular disease and mortality. In the last decade further research has expanded our understanding of the complex interaction of hyperglycemia with outcomes in patients with diabetes. Evidence has, in fact, shown that controlling blood glucose levels too tightly is associated with a paradoxical increase in cardiovascular deaths (yet fewer nonfatal cardiovascular events), although the mechanisms behind this pattern are still not conclusively understood. Furthermore, other research demonstrating the greater cardiovascular benefits of focusing on blood pressure and lipid lowering to obtain improvements in mortality and macrovascular disease in diabetes has led to a paradigm shift in the management of macrovascular disease. Observational and randomized controlled trial evidence has also supported a multifaceted approach concentrating not only on glycemia, but also on other established cardiovascular risk factors. These developments have led to international guidelines outlining the importance of specifically tailoring glycemic control to the individual and giving more importance to the management of blood pressure, cholesterol, and smoking cessation. This article reviews these developments in the management of type 2 diabetes mellitus, briefly discusses new paradigms resulting from recent trials, and highlights questions that remain unanswered and avenues that require further research.

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and various cancers, but the predominant cause is premature vascular deaths.\textsuperscript{2} Around 10\% of cardiovascular deaths in high-income countries are associated with diabetes.\textsuperscript{3}

In the last 20 years, remarkable reductions in diabetes cardiovascular complications have been noted and this is largely attributed to improved management of modifiable risk factors such as hypertension, lipid control, and smoking cessation, although glucose reductions and earlier diagnosis have also likely contributed (Figure 1).\textsuperscript{4}

Despite these improvements, rates of macrovascular disease in the diabetic population remain significantly higher than in the nondiabetic population. In the USA in 2010 the myocardial infarction rate in diabetics was 45.5 events per 10 000 population compared with 25.8 events per 10 000 population in nondiabetics.\textsuperscript{4} Similarly, in people with diabetes the stroke event rate was 52.9 per 10 000 population compared with 34.3 strokes per 10 000 population in people who did not have diabetes.\textsuperscript{4} The challenge remains not only to improve and lower this morbidity further without causing harm, but also to find a solution for the increasing prevalence of type 2 diabetes worldwide and prevent the rising levels of obesity. That noted, much of the rising prevalence of diabetes has been associated with improved survival so that more patients with diabetes are now living longer.\textsuperscript{5}

The conundrum of glycemic control
In 1998, the seminal UKPDS trial (United Kingdom Prospective Diabetes Study) demonstrated the benefits of intensive glucose control in type 2 diabetes patients, particularly with regard to microvascular benefit. Over 10 years, 3867 patients with newly diagnosed type 2 diabetes were treated with a sulfonylurea, metformin, or insulin to either conventional control (HbA\textsubscript{1c} of 7.9\% [6.9\%-8.8\%]) or intensive control (HbA\textsubscript{1c} of 7\% [6.9\%-8.8\%]).\textsuperscript{7} At 10 years in the intensive arm of the study there was a significant 25\% relative risk reduction in all microvascular disease and a nonsignificant trend of a 16\% risk reduction for myocardial infarction.\textsuperscript{6} Micro- and macrovascular disease though appeared to have differing relationships with glycemia, in that microvascular disease increased exponentially with higher levels of HbA\textsubscript{1c} whereas macrovascular disease increased with any elevation of glycemia above the normal range.\textsuperscript{7} Rather unexpectedly, patients treated with metformin had a 30\% risk reduction in myocardial infarction despite only showing a 0.6\% reduction in HbA\textsubscript{1c}, over the course of the study (which was less than the 0.9\% reduction observed for the whole study).\textsuperscript{8} After completion of the original study, in the 10-year-follow up of UKPDS the benefits on microvascular disease remained and a significant 15\% risk reduction in macrovascular disease became evident.\textsuperscript{9} This finding in the 10-year follow up suggests that whilst strong obvious initial benefits were gained in microvascular disease, metformin’s macrovascular benefits are likely sustained and become clearer over time. An important note about the UKPDS study is that was conducted in an era prior to the widespread use of statins and blood pressure–lowering agents. This did allow for easier assessment of the effect of glycemia on risk of comorbidities but care needs to be taken when comparing it with more recent trials where patients are often on statins and blood pressure–lowering medication.

UKPDS demonstrated a strong and direct relationship between glycemia and microvascular disease but since the correlation with macrovascular disease and mortality was less evident much research effort has gone into exploring this complex relationship in the last 10 to 15 years.

One of the most recent trials of glucose lowering in type 2 diabetes, the ACCORD trial (Action to Control Cardiovascular Risk in Diabetes), was actually terminated early after 3.5 years due to the higher cardiovascular mortality in the intensive treatment arm of the study.\textsuperscript{10} The HbA\textsubscript{1c} was 6.4\% (46 mmol/mol) in the intensive arm of the study, compared with 7.5\% (59 mmol/l) in the control group.\textsuperscript{11} There were higher rates of severe hypoglycemia in the intensive arm (10.5\% vs. 3.5\%), which may have affected cardiovascular outcomes and this is still broadly thought to be the most likely explanation.\textsuperscript{12} Other
The complex relationship between glycemia and cardiovascular risk has been difficult to extrapolate as initial presumptions were that elevated glycemia would have a direct causal relationship with cardiovascular risk. The Emerging Risk Factor Collaboration (ERFC) meta-analysis, which included 700,000 individuals, showed that fasting blood glucose was in fact nonlinearly and moderately associated with cardiovascular disease risk, whereas blood pressure and total cholesterol were more strongly and log-linearly associated with risk.\(^2\) Above a certain glycemic point, cardiovascular risk appears elevated but significant glycemia reductions below that threshold are unlikely to derive further significant benefits in cardiovascular risk.

Further studies support this and posttrial analyses of the ADVANCE study (Action in Diabetes and Vascular disease: Preter-Ax and DiamicroN MR Controlled Evaluation) suggested that above a certain baseline HbA\(_{1c}\) of 7% (53 mmol/mol), macrovascular events were increased by 38% but below that level there was no significant linear risk reduction.\(^2\) The baseline threshold for microvascular events in ADVANCE appeared to be lower at an HbA\(_{1c}\) of 6.5% (48 mmol/mol) above which point the risk of events increased by 40%.\(^1\) ADVANCE was published in 2008 (and included 11,140 participants) and by then a large number of participants were also on blood pressure– and lipid-lowering medications to control risk factors, unlike the UKPDS trial in the late 1990s. In total, these findings suggest that macrovascular risk due to dysglycemia in diabetes is clearer once HbA\(_{1c}\) is beyond around 7.0%, whereas microvascular risk escalates sooner than this, at the point of diagnosis.

The ORIGIN study (Outcome Reduction with an Initial Gliargine Intervention) adds further weight to the notion that lowering glycemia from a low baseline is not necessarily effective. Basal insulin glargine was added to normal diabetes care and by 7 years, at the end of the study, the intervention group had an HbA\(_{1c}\) of 6.2% (44 mmol/mol) compared with 6.5% (48 mmol/mol) in the control group.\(^1\) Both groups therefore had tight (below threshold) control of glycemia and an improvement in the HbA\(_{1c}\) by 0.3% but did not consequently reduce cardiovascular events.

Several meta-analyses have combined individual trial data and come to similar conclusions but added further insight into the glucose-risk relationship. A meta-analysis by Ray et al showed that for every 0.9% HbA\(_{1c}\) reduction over 5 years there was a 15% nonfatal myocardial infarction reduction and a 17% coronary heart disease reduction, but no improvements in overall mortality or stroke disease.\(^1\) Turnbull et al conducted a meta-analysis of four major studies of glucose lowering including UKPDS, ADVANCE, ACCORD, and VADT (Veterans Affairs Diabetes Trial). This meta-analysis additionally shows that patients with no prior history of vascular disease appeared to gain the most cardiovascular risk reduction with more aggressive glycemic control, and indicates that when vascular disease is already established marked reductions in glycemia are unlikely to significantly improve cardiovascular risk further.\(^1\)

It is therefore reasonable to aim for tight control and an HbA\(_{1c}\) of approximately 6.5% (48 mmol/mol) early in the course of type 2 diabetes; but as time progresses and in the elderly, or if comorbidities develop, it may be appropriate to relax this control to ~7% (53 mmol/mol) given the lack of any macrovascular benefit below this glycemic threshold and the possibility for increased harm. Glycemic control should therefore be individualized and several recent international diabetes guidelines including the Scottish Intercollegiate Guidelines Network (SIGN), National Institute for Health and Clinical Excellence (NICE), and American Diabetes Association (ADA) guidelines are in keeping with this.\(^1\)

Of course, whether trying to achieve tight control using newer glucose-lowering therapies gives different results to those seen with more established diabetes therapies requires future investigation. Perhaps most notably, another new paradigm has been opened up with the recent finding in the EMPA-REG outcome study which tested the cardiovascular benefits of empagliflozin—a sodium glucose-transporter 2 (SGLT2) inhibitor—in individuals with diabetes and existing cardiovascular disease. Very unexpectedly, there were striking reductions in cardiovascular and total mortality as well as in heart failure hospitalizations, whereas there were no significant benefits on nonfatal myocardial infarctions or stroke.\(^9\) In the study 7020 patients were treated over a median 3.1 years, and rates of death from cardiovascular cause were 3.7%, vs 5.9% in the placebo group (38% relative risk reduction), hospitalization for heart failure was 2.7% and 4.1%, respectively (35% relative risk reduction), and death from any cause 5.7% and 8.3%, respectively (32% relative risk reduction).\(^9\) The results could not be explained by a 0.3% difference in HbA\(_{1c}\), nor could they be explained by modest reductions in blood pressure and weight with active therapy. The pattern of effects and early separation in survival curves in Kaplan-Meier analyses also seem to suggest that the drug may be affecting hemodynamic processes early but not necessarily influencing atherothrombosis measurably, as least in this group of patients. Further work will urgently address the mechanisms and also address whether this is a class effect. In the meantime, it would appear that to lower cardiovascular disease in dia-
patients with type 2 diabetes.22 By 2006, the average total cholesterol was approximately 7.5 mmol/L in patients with type 2 diabetes.22 By 2006, the average total cholesterol was approximately 7.5 mmol/L in patients with type 2 diabetes.22 By 2006, the average total cholesterol was approximately 7.5 mmol/L in patients with type 2 diabetes.22 By 2006, the average total cholesterol was approximately 7.5 mmol/L in patients with type 2 diabetes.22 By 2006, the average total cholesterol was approximately 7.5 mmol/L in patients with type 2 diabetes.22

**Lipid-lowering benefits**

The benefits of lipid-lowering medications, particularly statins, have been shown to be as effective in both diabetic and non-diabetic groups of patients. There have been four major outcome trials involving diabetic patients or containing large numbers of diabetic patients that constitute this evidence base, including the HPS study (Heart Protection Study), ALLHAT-LLT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial-Lipid Lowering Trial), ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm), and CARDS (Collaborative Atorvastatin Diabetes Study). The CARDS study contained only diabetes patients but the other studies contained significant numbers of diabetes patients as subgroups for useful analysis.20 The CTT meta-analysis (Cholesterol Treatment Trialists) summarizes the main findings of these large studies and includes a total of 18,000 diabetic patients.21 For every 1 mmol/L decrease in low-density lipoprotein (LDL)-cholesterol there was a reduction in the combined endpoint of coronary heart disease–associated death and nonfatal myocardial infarction by 22%, hazard ratio 0.78 (99% CI [confidence interval], 0.69-0.87), cardiovascular disease events by 21%, hazard ratio 0.79 (99% CI, 0.72-0.86), vascular death by 13%, hazard ratio 0.87 (99% CI, 0.76-1.00), and all-cause death by 9%, hazard ratio 0.91 (99% CI, 0.82-1.01).21 What is notable is that statin benefits in relative terms were equal between groups with or without preexisting cardiovascular disease, but also in absolute terms the patients who gained most benefits were higher-risk patients on statins for secondary prevention. For instance, comparing the number of cardiovascular events per 1000 diabetes patients over 5 years if LDL-cholesterol was lowered using a statin by 1 mmol/L, there would be a reduction in the number of events by 57 when used for secondary prevention compared with 36 fewer events when used for primary prevention.21

In line with the accumulating evidence of substantial cardiovascular benefits of statins in diabetes, cholesterol levels have been falling in keeping with rising prescription rates. In our review of many diabetes trials that roughly averaged around the 1990s, the average total cholesterol was approximately 5.4 mmol/L in patients with type 2 diabetes.22 By 2006, the average cholesterol levels had declined to 4.5 mmol/L, with a further fall to 4.2 mmol/L by 2008.22

Most national and international guidelines now recommend that modest doses of statins be prescribed to all patients with type 2 diabetes above the age of 40 years of age.17 More intensive statin doses can be targeted to those at highest risk of subsequent events. This includes those with diabetes and preexisting cardiovascular disease (a group we showed to be at markedly increased chances of premature mortality) or those with evidence of proteinuria or chronic kidney disease.23 Further guidance or research is needed to establish when to prescribe statins to younger individuals with type 2 diabetes.

The evidence for statins is therefore strong, but up until recently other lipid agents had failed to show any benefits in diabetes. The FIELD study (Fenofibrate Intervention and Event Lowering in Diabetes) assessed fenofibrate use in diabetes, and although there was a significant decrease in nonfatal myocardial infarction there was a paradoxical increase in all-cause mortality.24 In 2010, the ACCORD study added fenofibrate or placebo to simvastatin and did not show any significant gains in all-cause mortality or cardiovascular morbidity.25 That noted, in the recently published IMPROVE-IT trial (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial), which compared combination therapy of daily ezetimibe and simvastatin with simvastatin monotherapy in patients following a recent acute coronary syndrome, in the subgroup of diabetes patients (n=4933) ezetimibe therapy led to a further 0.4 mmol/L lowering of LDL-cholesterol and a 14% reduction in major cardiovascular events.26 These results establish ezetimibe as an evidence-based add-on to statins in patients with diabetes who fail to meet targets on statin therapy.

**Blood pressure and the renin-angiotensin-aldosterone system**

Hypertension is strongly linearly related to increased risk of all diabetes-related comorbidities as clearly shown in the UKPDS 36 trial.27 For every 10-mm Hg decrease in mean systolic blood pressure there was an 11% risk reduction in myocardial infarction, a 13% reduction in microvascular events, a 15% decrease in diabetes-related deaths, and a 12% reduction for any complication relating to diabetes.27 In 2009, Ray et al showed in their meta-analysis the respective benefits that glycemic control, reduction in LDL-cholesterol, and blood pressure lowering each have in reducing cardiovascular events (Figure 2, page 24).14

It is clear that the impact of hypertension on diabetes-associated cardiovascular risk is strong, further emphasizing the need to prioritize blood pressure and lipid control with statins early in patients with type 2 diabetes. That is not to say that glycemic control is not important, but merely concentrating on good glycemic control alone will have less impact on cardiovascular events and mortality than blood pressure or lipid control. The evidence for hypertension association is therefore strong, but what has been more difficult to ascertain has been the optimal point at which to treat blood pressure and what blood pressure target to aim for. This has been disputed overs the last 10 years, but recently the extensive meta-analysis by Emdin et al published in 2015 has helped support a cut-off point at which benefit of treating blood pressure in pa-
Patients with type 2 diabetes should be gained. A total of 40 blood pressure trials including 100,354 diabetes patients were included in the meta-analysis, and in keeping with previous research, for every elevation in systolic blood pressure by 10 mm Hg there was a corresponding increase in complications. What this review added was a clear cut-off point which showed that treating a systolic blood pressure greater than 140 mm Hg improved all outcomes, as shown in Figure 3.

In all diabetes-associated outcomes there was strong evidence supporting treating blood pressure above 140 mm Hg (systolic), but for some outcomes such as stroke, retinopathy, or albuminuria there was also benefit in treating hypertension when baseline systolic blood pressure was less than 140 mm Hg, so targets of near 130 mm Hg may be useful in selecting patients at elevated risks of these latter complications.

Figure 2. Relative benefits of glucose lowering, blood pressure lowering, and low-density lipoprotein–cholesterol lowering on cardiovascular events per 200 diabetes patients treated for 5 years.


Figure 3. Standardized associations between 10–mm Hg lower systolic blood pressure and all-cause mortality, macrovascular outcomes, and microvascular outcomes stratified by mean systolic blood pressure of trial participants at entry.

Macrovascular outcomes include cardiovascular events, coronary heart disease, stroke, and heart failure; and microvascular outcomes include renal failure, retinopathy, and albuminuria. Mean baseline blood pressure is weighted by number of participants. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines indicate 95% CIs of the estimate.

A slightly different aspect of blood pressure-lowering agent use in diabetes relates to the inhibition of the renin-angiotensin-aldosterone system. Both angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have been shown in a large meta-analysis to significantly reduce the progression of diabetic kidney disease, irrespective of blood pressure. ACE inhibitors reduced the progression of microalbuminuria by 45%, a relative risk reduction of 0.55 (95% CI, 0.26-0.71), and ARBs reduced the progression by 51%, a relative risk reduction of 0.49 (95% CI, 0.32-1.05). They also reduced the progression to end-stage renal failure, which is obviously the most important potential consequence of diabetes-related microvascular kidney disease. Accordingly, ACE inhibitors and ARBs are prioritized early in hypertension algorithms for patients with diabetes, but it is important to note that all blood pressure-lowering medications work to lessen the risk and no classes should be avoided (unless there are specific contraindications) if blood pressure levels remain elevated. Interestingly, in the Emdin meta-analysis, it appeared that calcium channel blockers showed slightly more benefit in lowering the risk of stroke, whereas ACE inhibitors/ARBs or diuretics did more to lower the risk of heart failure.

**Multi-intervention management for diabetes**

We have so far focused mainly on isolated glycemic or risk factor control but it is clear that maximal impact will occur when these separate interventions are combined. In the last 5 years, observational evidence supports significant gains in cardiovascular disease reduction and mortality via this approach in diabetes. The National Health And Nutrition Examination Survey (NHANES) looked at data from 1999-2008 and included 1977 participants with diabetes aged 30-74. Durin this period the Framingham heart study predicted that during this 8-year period the Framingham heart study predicted that the 10-year risk would decrease significantly as can be seen in Figure 4.

The reasons for the significant decreases in the risk of developing heart disease can be attributed to several factors during this 8-year period. In the male participants the total cholesterol was reduced to 4.6 mmol/L from 5.3 mmol/L during this period, and rates of smoking declined to 15% from 20%. HbA1c improved to 7.3% from 7.7%, and the average systolic blood pressure went down to 128.7 mm Hg from 130.5 mm Hg in 1999-2000. These significant reductions and improvements were also noted in the female participants of the study. This observational evidence base showed the improvements that had been made in a large number of patients over a prolonged period of time.

In 2008, the seminal STENO-2 study provided early randomized controlled data to support a multifactorial approach to diabetes, albeit in a modest number of patients. In the STENO-2 study, 160 participants were randomized to either standard care or intensive care which included the following targets: an HbA1c of 6.5% (48 mmol/mol), blood pressure of <130/80, total cholesterol <4.5 mmol/L, triglycerides <1.7 mmol/L.

In the intervention group patients with microalbuminuria were also given blockers of the renin-angiotensin-aldosterone system, regardless of blood pressure, and low-dose primary prevention aspirin. The follow-up period for STENO-2 was 13.3 years and the absolute risk reduction for death in the intervention group was 20%, hazard ratio 0.54 (95% CI,0.32 to 0.89; P=0.02), and the absolute risk reduction for death due to cardiovascular causes was 13%, hazard ratio 0.43 (95% CI, 0.19 to 0.94; P=0.04). During the study there were no significant differences and changes in behavior between the groups with regard to smoking, exercise, diet, and weight, which suggests that the primary gains were made through medical management of cholesterol, blood pressure, and glycemia. Whether the addition of aspirin also added benefit is not clear, and the current evidence base would suggest that aspirin should be used only for secondary prevention in patients with or without diabetes.

**Bringing it all together**

In 2012, we produced a table (Table I, page 26) to conceptualize the relative impact of glucose, blood pressure, and lipid control on diabetes complications as well as the cost of use and complexity of the respective drug regimens. The table...
suggests that on the one hand cardiovascular risk reduction is more impacted by lipid and blood pressure lowering, whereas glucose reduction has a slow burn effect.32 By contrast, glucose and blood pressure lowering are more important in lowering microvascular risks. Of course, the recent EMPA-REG outcomes trial adds a new twist to the story for patients with diabetes and cardiovascular disease, suggesting that

**Summary and going forward**

The aforementioned trials have highlighted the benefits of a multifactorial approach to the management of diabetes, with particular emphasis on the importance of managing lipids and blood pressure to reduce cardiovascular disease. However, what remains less certain is the extent to which microvascular and macrovascular risk can be further improved and if there are other pathways or mechanisms (perhaps subclinical fluid overload in those with diabetes and cardiovascular disease, potentially revealed by EMPA-REG outcomes) to further improve morbidity and mortality.

A final point to note is that we are largely failing in tackling obesity through changes in lifestyle in patients with diabetes or at elevated risk for diabetes. Many countries are also facing rising obesity levels generally. Lifestyle management is an area in need of further research since tackling obesity not only improves risk factors but importantly improves patients’ quality of life. Furthermore, if we can even delay diabetes for a few years in those noted to be at elevated risk, the benefits to patients are enormous since mounting evidence indicates that the younger one develops diabetes, the higher the future risks are.33

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### Table 1. Relative benefits on diabetes-associated outcomes (+ low/modest, ++ significant) and relative cost of use and complexity (+ low, ++ moderate, +++ high) of glucose lowering, blood pressure lowering, and statins.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Low/modest (GL)</th>
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<th>GL vs BP</th>
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<tr>
<td>Complexity</td>
<td>+++</td>
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</tr>
</tbody>
</table>

*Signifies areas of on-going research or where more research is required.

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### References

19. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes Trial adds a new twist to the story for patients with diabetes and cardiovascular disease, suggesting that SGLT2 inhibitors may be particularly apt at lowering cardiovascular death and heart failure risks in this group of patients.32

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### Table 1

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### Summary and going forward

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changing the natural history of type 2 diabetes: implications for clinical care

The importance of a multi-faceted approach in type 2 diabetes – Sattar and McLaren

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Keywords: blood pressure; cardiovascular disease; cholesterol; glycemia; risk factor modification; type 2 diabetes

L'IMPORTANCE D'UN TRAITEMENT MULTIFACTORIEL COMPLET DU DIABÈTE DE TYPE 2

Historiquement, le traitement du diabète a privilégié le contrôle glycémique comme méthode principale de réduction de la morbi-mortalité liée au diabète par rapport à d’autres facteurs métaboliques et physiopathologiques. La caractéristique principale du diabète étant une élévation de la glycémie, une quasi-normalisation de la glycémie était supposée améliorer considérablement, voir éviter, les comorbidités. Les résultats de l’étude phare du diabète de type 2, l’UKPDS (United Kingdom Prospective Diabetes Study), ne sont cependant pas complètement en accord avec cette hypothèse. Bien que cette étude ait démontré les effets bénéfiques significatifs du contrôle glycémique sur la diminution des complications microvasculaires, ce ne fut pas le cas pour les maladies macrovasculaires et la mortalité. Ces 10 dernières années, la recherche a permis de mieux comprendre l’interaction complexe entre l’hyperglycémie et ses conséquences chez les diabétiques. Il a en fait été montré qu’un contrôle trop sévère de la glycémie est associé à une augmentation paradoxale du nombre de décès d’origine cardio-vasculaire (avec cependant moins d’événements cardio-vasculaires non fatals), les mécanismes sous-jacents n’étant pas encore définitivement compris. De plus, d’autres données démontrant les avantages accrus sur le plan cardio-vasculaire d’une approche visant à la fois l’abaissement de la pression artérielle et des lipides pour améliorer la mortalité et la maladie macrovasculaire dans le diabète, ont entrainé un changement radical de la prise en charge de cette maladie. Des données issues d’études observationnelles, contrôlées, et randomisées confirment également l’intérêt d’avoir une approche diversifiée, centrée non seulement sur la glycémie, mais aussi sur d’autres facteurs de risque cardio-vasculaire connus. Ces avancées ont conduit les recommandations internationales à souligner l’importance d’adapter le contrôle glycémique à chaque patient, et à accorder plus d’importance à la prise en charge de la pression artérielle, du cholestérol et du sevrage tabagique. Cet article passe en revue les avancées dans la prise en charge du diabète de type 2, analyse brièvement les nouveaux modèles issus des résultats d’études récentes et souligne les questions qui restent encore sans réponse ainsi que les pistes nécessitant des recherches plus poussées.
People with type 2 diabetes have a significantly higher risk of developing cardiovascular disease compared with the general population, which is important because this is a leading cause of morbidity and mortality. Although the glucose-lowering benefits of oral antidiabetic drugs have been well established in clinical trials, some of these drugs have been associated with an increased risk of cardiovascular events. Perhaps the most well-known example of this association is the link between rosiglitazone and risk of heart failure and myocardial infarction. There are also cardiovascular safety questions associated with sulfonylureas and our understanding of the cardiovascular safety of newer oral antidiabetic classes (dipeptidyl peptidase 4 inhibitors and sodium glucose cotransporter-2 inhibitors) is evolving. In contrast, metformin and acarbose do not appear to be associated with adverse cardiovascular events. Questions about cardiovascular safety prompted the Food and Drug Administration in the United States to require cardiovascular safety trials as part of the approval process for new antidiabetic drugs. In addition, there have been a large number of observational studies, randomized controlled trials, and meta-analyses examining the cardiovascular safety of antidiabetic drugs. This review examines the current issues and evidence related to cardiovascular safety for each class of oral antidiabetic drug. Understanding the potential cardiovascular risk associated with these drugs will help clinicians and patients with treatment decisions for type 2 diabetes.

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Changing the natural history of type 2 diabetes: implications for clinical care

Cardiovascular safety of oral antidiabetic drugs

by S. H. Simpson, Canada

Over 90% of people with diabetes have type 2 diabetes, which carries with it a twofold higher risk of adverse cardiovascular events, such as myocardial infarction, stroke, and heart failure compared with people without diabetes.1 In addition, the risk of all-cause death and cardiovascular-related death is significantly higher in people with diabetes compared with those without diabetes.2 The heightened risk of cardiovascular disease in people with diabetes is likely due to a clustering of cardiovascular risk factors, including obesity, hypertension, and dyslipidemia.3,4 Since cardiovascular disease is a leading cause of morbidity and mortality in people with diabetes,3 it is imperative that clinicians consider the cardiovascular implications of their treatment decisions.

As glycemic control remains an important focal point for type 2 diabetes management, the majority of patients will require oral antidiabetic drugs to control hyperglycemia.5,6 Generally, there is strong clinical trial evidence demonstrating that oral

Credit: Christy Dean Photography
antidiabetic drugs reduce hyperglycemia to a similar degree and significantly decrease the risk of microvascular complications.\textsuperscript{6,8} However, the strategy used to reduce blood glucose may affect a patient’s cardiovascular risk. For example, in the ACCORD study (Action to Control Cardiovascular Risk in Diabetes), patients with a median 10-year history of type 2 diabetes and mean HbA\textsubscript{1c} of 8.3% were treated to rapidly achieve glycemic targets of 6.0% (intervention group) or maintain their current glycemic control.\textsuperscript{9} Although the ACCORD study did not find a difference in the primary outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, there was a significantly higher rate of all-cause mortality in the intervention group compared with controls. Other studies examining intensive glycemic control strategies did not find a significant effect on cardiovascular risk (Table I).\textsuperscript{10-14}

Despite this evolving evidence from intensive glycemic control studies, there is still uncertainty about possible cardiovascular effects related to type 2 diabetes management, especially regarding some oral antidiabetic drugs. For example, questions of cardiovascular safety for sulfonylureas have been circulating for over 40 years.\textsuperscript{15} The issue of cardiovascular safety gained substantial prominence when a link between rosiglitazone and risk of myocardial infarction was demonstrated.\textsuperscript{16} Indeed, concerns about the cardiovascular safety of antidiabetic drugs prompted the Food and Drug Association (FDA) in the United States (US) to require cardiovascular safety trials as part of the approval process for new antidiabetic drugs.\textsuperscript{17}

Since publication of the Guidance for Industry document by the US FDA,\textsuperscript{17} a large number of observational studies, randomized controlled trials, and meta-analyses have been conducted...
ducted to examine the cardiovascular safety of antidiabetic drugs. Most studies have used the composite of a major adverse cardiovascular event (MACE), which includes cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke as the primary outcome, while others have examined the effect of antidiabetic drugs on cardiovascular risk factors (blood pressure, weight, and lipid levels). The purpose of this review is to examine the current issues and evidence related to cardiovascular safety for each class of oral antidiabetic drug.

Acarbose
Acarbose inhibits the α-glucosidase enzyme, which breaks down complex carbohydrates into monosaccharides that are rapidly absorbed from the gastrointestinal tract. When taken with meals, acarbose will effectively reduce postprandial glucose levels and help manage hyperglycemia. Initial reviews of the placebo-controlled studies suggested that acarbose use was associated with a significantly lower risk of myocardial infarction and other cardiovascular events. This reduction in cardiovascular risk was thought to be linked to reductions in blood pressure, postprandial hyperglycemia, and lipid levels, as well as a neutral effect on weight. However, a more comprehensive review of the literature was unable to find a difference in cardiovascular risk associated with any α-glucosidase inhibitors, including acarbose.

While acarbose may have a neutral effect on body weight gain and other oral antidiabetic drugs like sulfonylureas and thiazolidinediones are associated with significant increases in weight, very few people with type 2 diabetes use this drug. Two major factors may explain the limited use of acarbose. First, relative to other oral antidiabetic drugs, acarbose is not as effective at lowering blood glucose. Second, and perhaps more importantly, significant gastrointestinal side effects like cramping and flatulence are quite undesirable and lead to substantial rates of treatment discontinuation.

Metformin
The exact mechanism of action for metformin is still not fully understood, though this drug reduces glucose production in the liver and affects adenosine 5’-monophosphate-activated protein kinase (AMPK) activity, a major cellular regulator of energy metabolism. Clinical practice guidelines recommend using metformin as a first-line agent because of its proven beneficial effects on hyperglycemia and risk of microvascular complications, neutral effect on weight, minimal risk of hypoglycemia, and favorable safety profile. Although lactic acidosis was a significant concern with an earlier biguanide, phenformin, after more than 50 years of clinical experience, there is no evidence to support a link with metformin.

Two clinical trials have randomly allocated patients to metformin or a comparator and evaluated the risk of cardiovascular outcomes. In both studies, patients allocated to metformin use experienced significantly lower rates of cardiovascular events. Metformin has also been shown to significantly reduce lipid levels. More recently, interest in metformin has shifted to an examination of its safety in patients with heart failure. Renal dysfunction and heart failure have been long-standing contraindications for metformin use because of the perceived risk of lactic acidosis. However, there is good evidence that metformin is used in patients with these contraindications, with no change in the incidence of lactic acidosis. Moreover, observational studies have demonstrated that metformin use in patients with heart failure is associated with a lower risk of cardiovascular morbidity and mortality. It is also important to note that none of the patients allocated to metformin use in the UKPDS study (United Kingdom Prospective Diabetes Study) developed lactic acidosis. These observations may be influencing requests to regulatory agencies to revisit previous restrictions on metformin use in patients with heart failure or reduced renal function.

Thiazolidinediones
Thiazolidinediones bind to peroxisome proliferator-activated receptor-γ, leading to receptor upregulation and improved insulin sensitivity in muscle, liver, and fat tissue. These drugs produce a significant reduction in blood glucose with minimal risk of hypoglycemia. Initial observations with thiazolidinediones suggested beneficial effects on blood pressure and lipid levels and early clinical trials reported possible reductions in cardiovascular events. In 2007, however, evidence emerged linking rosiglitazone to an increased risk of myocardial infarction and death. This observation was soon replicated by others and extended to include an association with heart failure risk. As these retrospective analyses were hypothesis-generating, a cardiovascular outcome trial was conducted to compare addition of rosiglitazone with metformin or sulfonylurea monotherapy with the combination of metformin and sulfonylurea. This study demonstrated that the risk of cardiovascular death or hospitalization for myocardial infarction or stroke was similar between treatment groups. However, hospitalization or death attributable to heart failure was significantly higher in patients allocated to rosiglitazone use.

Although pioglitazone does not appear to have the same level of cardiovascular risk as rosiglitazone, there appears to be a higher risk of fractures and cancer. Thiazolidinediones are also associated with fluid retention and significant weight gain. Introduction of other classes of antidiabetic drugs, along with concerns of the various adverse effects are likely behind the observed decline in thiazolidinedione use over the past few years.

Sulfonylureas and nonsulfonylurea secretagogues
Sulfonylureas and nonsulfonylurea secretagogues bind to sulfonylurea receptors on pancreatic β-cells and promote insulin release by closing ATP-sensitive potassium (K<sub>ATP</sub>) chan-
nents.\textsuperscript{35,36} These drugs are commonly used to help control hyperglycemia in type 2 diabetes and their popularity is likely due to decades of experience, strong evidence demonstrating efficacy, and familiarity with known side effects of hypoglycemia and weight gain.\textsuperscript{12,15,21-23} Interestingly, sulfonylureas are frequently used even though questions of cardiovascular safety were raised over 40 years ago.\textsuperscript{15} Concern began when the University Group Diabetes Program (UGDP) investigators reported a significantly higher rate of cardiovascular deaths in patients using tolbutamide compared with placebo.\textsuperscript{34} The UKPDS seemed to quell these concerns when similar rates of myocardial infarction, stroke, and death were reported in patients using a sulfonylurea for intensive treatment compared with conventional treatment.\textsuperscript{25} It is important to note, however, that the UKPDS tested glucose targets and by the end of the study many patients in the conventional treatment arm were using sulfonylureas to maintain a fasting blood glucose level <15 mmol/L.\textsuperscript{26} Thus, the question of cardiovascular safety remains unanswered in clinical trials.

Given the uncertainty surrounding sulfonylurea cardiovascular safety, it is not surprising that there have been numerous observational studies and post hoc analyses of randomized controlled trials examining this issue. Observations from these studies have been summarized in 7 meta-analyses (Table II).\textsuperscript{25,36-41} Although summaries from randomized controlled trials would suggest there is no significant difference in cardiovascular risk between sulfonylureas and comparators, it is important to note that almost all of these studies were small and were short-term evaluations of glycemic response to therapy. Therefore, these studies were neither designed nor adequately powered to examine a cardiovascular safety question.\textsuperscript{34} In contrast, observational studies may be large enough to detect differences in cardiovascular risk, but their designs have well-known limitations and results should be considered hypothesis-generating. Collectively, these studies provide some evidence that risk of cardiovascular events may be higher in people taking sulfonylureas compared with other antidiabetic drugs. However, this hypothesis should be tested in a properly designed trial. Although two ongoing trials are designed to compare the cardiovascular risk between sulfonylureas and other oral antidiabetic drugs, these studies may not completely answer the safety question since there is no placebo arm.\textsuperscript{42,43}

Two biological mechanisms may explain why the risk of adverse cardiovascular events is higher in patients using sulfonylureas. First, hypoglycemia leads to alterations in myocyte physiology, which will prolong the QT interval and increase the risk of disrhythmias.\textsuperscript{44,45} In addition, catecholamine release in response to hypoglycemia can promote vasoconstriction and tachycardia, which in turn increases the risk of myocardial ischemia.\textsuperscript{44,46} Hypoglycemia is a well-recognized adverse effect of all oral antidiabetic agents and occurs most frequently with sulfonylureas.\textsuperscript{47} Although few studies have directly compared the risk of hypoglycemia between sulfonylureas, a systematic review and meta-analysis of these data reported that glyburide had the highest risk among sulfonylureas.\textsuperscript{48} The sec-

<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>Design of included studies (n)</th>
<th>Comparators</th>
<th>Outcome</th>
<th>Pooled estimate (95% CI)</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selvin (2008)\textsuperscript{25}</td>
<td>RCT (5)</td>
<td>SU versus any comparator</td>
<td>CV morbidity</td>
<td>0.89 (0.71-1.11)</td>
<td>I\textsuperscript{2}=0.40</td>
</tr>
<tr>
<td></td>
<td>RCT (5)</td>
<td>SU versus any comparator</td>
<td>CV mortality</td>
<td>0.92 (0.88-1.26)</td>
<td>I\textsuperscript{2}=0.97</td>
</tr>
<tr>
<td></td>
<td>RCT (6)</td>
<td>SU versus any comparator</td>
<td>All-cause mortality</td>
<td>0.90 (0.70-1.15)</td>
<td>I\textsuperscript{2}=0.99</td>
</tr>
<tr>
<td>Monani (2013)\textsuperscript{36}</td>
<td>RCT (30)</td>
<td>SU versus any comparator</td>
<td>MACE</td>
<td>1.08 (0.86-1.36)</td>
<td>I\textsuperscript{2}=49%</td>
</tr>
<tr>
<td></td>
<td>RCT (23)</td>
<td>SU versus any comparator</td>
<td>CV mortality</td>
<td>1.40 (0.87-2.26)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>RCT (37)</td>
<td>SU versus any comparator</td>
<td>All-cause mortality</td>
<td>1.22 (1.01-1.49)</td>
<td>NR</td>
</tr>
<tr>
<td>Hemmingsen (2013)\textsuperscript{37}</td>
<td>RCT (4)</td>
<td>SU versus metformin</td>
<td>CV morbidity</td>
<td>0.67 (0.48-0.93)</td>
<td>I\textsuperscript{2}=0%</td>
</tr>
<tr>
<td></td>
<td>RCT (8)</td>
<td>SU versus metformin</td>
<td>CV mortality</td>
<td>1.47 (0.53-4.01)</td>
<td>I\textsuperscript{2}=0%</td>
</tr>
<tr>
<td></td>
<td>RCT (8)</td>
<td>SU versus metformin</td>
<td>All-cause mortality</td>
<td>0.98 (0.61-1.58)</td>
<td>I\textsuperscript{2}=0%</td>
</tr>
<tr>
<td>Landman (2014)\textsuperscript{38}</td>
<td>RCT (9)</td>
<td>Gliclazide versus any comparator</td>
<td>CV events</td>
<td>0.95 (0.57-1.61)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>RCT (15)</td>
<td>Gliclazide versus any comparator</td>
<td>CV mortality</td>
<td>0.81 (0.26-2.47)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>RCT (17)</td>
<td>Gliclazide versus any comparator</td>
<td>All-cause mortality</td>
<td>1.50 (0.62-3.62)</td>
<td>NR</td>
</tr>
<tr>
<td>Zhang (2014)\textsuperscript{39}</td>
<td>RCT (4)</td>
<td>SU versus DPP4 inhibitors</td>
<td>CV events</td>
<td>1.89 (1.15-3.13)</td>
<td>I\textsuperscript{2}=0%</td>
</tr>
<tr>
<td>Phung (2013)\textsuperscript{40}</td>
<td>RCT (7)</td>
<td>SU versus no SU</td>
<td>CV mortality</td>
<td>1.22 (0.63-2.39)</td>
<td>I\textsuperscript{2}=0%</td>
</tr>
<tr>
<td></td>
<td>Observational (20)</td>
<td>SU versus no SU</td>
<td>CV mortality</td>
<td>1.26 (1.10-1.44)</td>
<td>I\textsuperscript{2}=25%</td>
</tr>
<tr>
<td>Forst (2013)\textsuperscript{41}</td>
<td>Observational (4)</td>
<td>SU versus no SU</td>
<td>CV mortality</td>
<td>2.72 (1.95-3.79)</td>
<td>I\textsuperscript{2}=96%</td>
</tr>
<tr>
<td></td>
<td>Observational (12)</td>
<td>SU versus no SU</td>
<td>All-cause mortality</td>
<td>1.92 (1.48-2.49)</td>
<td>I\textsuperscript{2}=97%</td>
</tr>
</tbody>
</table>

Table II. Meta-analyses examining the association between sulfonylureas and cardiovascular events.

Abbreviations: CV, cardiovascular; DPP4, dipeptidyl peptidase 4; MACE, major cardiovascular event; NR, not reported; RCT, randomized controlled trial; SU, sulfonylurea.

Based on data from references 25 and 36-41.
Dipeptidyl peptidase 4 (DPP4) inhibitors reduce metabolism of glucagon-like peptide-1 (GLP-1), a hormone released by the small intestine in response to meals. Inhibition of GLP-1 metabolism increases GLP-1 circulating levels, which in turn potentiates the release of insulin and reduces the postprandial rise in blood glucose. In premarketing clinical trials, DPP4 inhibitors provided similar reductions in blood glucose compared with other oral antidiabetic drugs. The major side effects of these drugs appeared to be gastrointestinal and possible safety concerns with pancreatitis and pancreatic neoplasia; however, since this class of drug was introduced at the time of the changes in FDA requirements for approval, additional cardiovascular safety trials were initiated for alogliptin, linagliptin, saxagliptin, and sitagliptin.

Cardiovascular safety studies mandated in the 2008 FDA requirements must demonstrate that a new antidiabetic drug is safe, or in other words, does not increase the risk of cardiovascular events beyond an acceptable threshold. Unlike traditional cardiovascular outcome studies that are designed to find benefit, safety trials must demonstrate that the new drug is not inferior when compared with placebo. Since the antidiabetic drug investigated in these studies will affect glucose levels, patients in both groups are treated to maintain similar levels of glycemic control. Clinicians are allowed to change background antidiabetic regimens at their discretion during the study. A cardiovascular safety trial is considered successful if there is no significant difference in risk of events between treatment and placebo groups and the upper limit of the 95% confidence interval does not cross 1.3.

Three cardiovascular safety trials of DPP4 inhibitors have been published and a fourth study is ongoing, with results expected in 2018 (Table III). In general, these studies enrolled patients with type 2 diabetes and an elevated level of cardiovascular risk (Figure 2). At the end of the three published trials, glycemic control was slightly better in the DPP4 treatment groups compared with placebo (P < 0.001 for all comparisons); however, none of the differences in HbA1c reached a clinically important difference of >0.5%. Regarding the primary outcome of cardiovascular safety, all three studies demonstrated noninferiority versus placebo, with upper limits of the 95% confidence intervals <1.3 (Table III). The study examining saxagliptin did observe a significantly higher rate of hospitalization for heart failure compared with placebo; however, this observation has not been replicated in other clinical trials. At this point it is uncertain if the observed risk of heart failure is a true safety signal or due to random error.

**SGLT-2 inhibitors**

Sodium glucose cotransporter-2 (SGLT-2) inhibitors reduce hyperglycemia in people with type 2 diabetes by decreasing glucose reabsorption in the renal tubule. In premarketing clinical trials, SGLT-2 inhibitors significantly reduced blood glucose with a low risk of hypoglycemia. These agents also had favorable effects on cardiovascular risk factors by reducing body weight and blood pressure. The major side effect...
observed in these trials was an increased risk of urinary tract infections. In addition, there are emerging questions of ketoacidosis, which has led to a safety warning issued by the US FDA.61

Decreasing glucose reabsorption in the kidneys produces glycosuria, resulting in a loss of 200-300 kilocalories per day.62 Clinical trials have consistently demonstrated a weight reduction associated with SGLT-2 inhibitor use, with the weighted mean difference in body weight reduction from baseline ranging from 1.7 to 1.9 kilograms when compared with placebo and 1.1 kilograms when compared with sulfonylureas.60 From these studies, it appears that weight loss occurs primarily in the first 3 to 6 months of therapy and then remains stable for the duration of the observation period. In addition to weight loss, important changes in visceral fat mass also occur. Body composition studies of 1 to 2 years’ duration have shown that the reduction in weight associated with SGLT-2 inhibitor use was due to reductions in visceral fat or subcutaneous fat.60-65 The contributions of visceral fat changes to cardiovascular risk remain unknown, however.66

The weighted mean difference in systolic blood pressure reduction ranged from 3 to 5 mm Hg when SGLT-2 inhibitors were compared with placebo, while diastolic blood pressure decreased by 2 mm Hg.60 An important observation from these studies is that heart rate did not increase in response to the lower blood pressure. The mechanism for the blood pressure reduction, however, is not known, though the mild diuresis associated with SGLT-2 inhibitor use may play a role.66

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**Figure 2.** Baseline cardiovascular risk of patients enrolled in cardio-vascular outcome trials.

Abbreviations: CANVAS, CANagliflozin cardioVascular Assessment Study; CARMELINA, Cardiovascular and Renal Microvascular outcome study with LINagliptin; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Outcomes - Thrombolysis In Myocardial Infarction; EMPA-REG Outcome, empagliflozin cardiovascular outcome event trial in type 2 diabetes mellitus patients; EXAMINE, Examination of Cardiovascular Outcomes with Albiglutin versus standard care; HDL-C, high-density lipoprotein cholesterol; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus-Thrombolysis In Myocardial Infarction; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin.

Based on data from references 55-58 and 67-69.
Currently there are four clinical trials examining the risk of cardiovascular events with SGLT-2 inhibitor use compared with placebo in patients at high risk of cardiovascular events (Table III; Figure 2). While the EMPA-REG Outcome™ study is now completed, the remaining three studies will not produce results for several years. All studies are using MACE as the primary outcome, with the exception of EMPA-REG Outcome™, which included hospitalization for unstable angina in the composite outcome.

Conclusion
Risk of cardiovascular disease is an important consideration for clinicians when managing patients with type 2 diabetes. Although most oral antidiabetic drugs have similar effects on hyperglycemia and reduce the risk of microvascular complications, there are cardiovascular safety concerns associated with some of these drugs. Understanding the potential cardiovascular risk associated with oral antidiabetic drugs will help clinicians and patients with treatment decisions for type 2 diabetes. Overall, metformin appears to have the best benefit-to-risk profile, which is consistent with its place as first-line therapy in clinical practice guideline recommendations. Acarbose does not appear to increase the risk of adverse cardiovascular events; however, the unfavorable gastrointestinal side effects limit its usefulness in type 2 diabetes management. Newer classes of oral antidiabetic drugs—the DPP4 inhibitors and SGLT2 inhibitors—do not appear to increase the risk of adverse cardiovascular events, though the evidence to support this premise is still evolving. Current evidence suggests that sulfonylurea use is associated with an increased risk of adverse cardiovascular events; however, this risk varies among individual drugs, with the lowest risk associated with gliclazide. Thiazolidinediones, especially rosiglitazone, increase the risk of heart failure, stroke, and myocardial infarction and therefore should be avoided in patients at risk of cardiovascular disease.

Table III. Cardiovascular outcome trials.

<table>
<thead>
<tr>
<th>Study</th>
<th>Clinicaltrials.gov</th>
<th>Intervention</th>
<th>Enrolment</th>
<th>Primary Outcome</th>
<th>Follow-up</th>
<th>Results*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DPP4 Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXAMINE55,56</td>
<td>NCT00968708</td>
<td>Alogliptin</td>
<td>5380</td>
<td>MACE</td>
<td>median 1.5 years</td>
<td>Primary: 0.96 (UL 1.16)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HF: 1.07 (0.79-1.46)</td>
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<tr>
<td>SAVOR-TIMI 53</td>
<td>NCT01107886</td>
<td>Saxagliptin</td>
<td>16 492</td>
<td>MACE</td>
<td>median 2.1 years</td>
<td>Primary: 1.00 (0.89-1.12)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HF: 1.27 (1.07-1.51)</td>
</tr>
<tr>
<td>TECOS93</td>
<td>NCT00790205</td>
<td>Sitagliptin</td>
<td>14 671</td>
<td>MACE plus UA</td>
<td>median 3.0 years</td>
<td>Primary: 0.98 (0.88-1.09)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>hospitalization</td>
<td></td>
<td>HF: 1.00 (0.83-1.20)</td>
</tr>
<tr>
<td>CARMELINA</td>
<td>NCT01897532</td>
<td>Linagliptin</td>
<td>8300</td>
<td>MACE plus UA</td>
<td>completion in 2018</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>hospitalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SGLT-2 Inhibitors</strong></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>EMPA-REG Outcome™68,69</td>
<td>NCT01131676</td>
<td>Empagliflozin</td>
<td>7097</td>
<td>MACE plus UA</td>
<td>completed May 2015</td>
<td>Primary: 0.86 (0.74-0.99)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>hospitalization</td>
<td></td>
<td>HF: 0.65 (0.50-0.85)</td>
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<tr>
<td>CANVAS67</td>
<td>NCT01032629</td>
<td>Canagliflozin</td>
<td>4407</td>
<td>MACE</td>
<td>completion in 2017</td>
<td></td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>NCT01730534</td>
<td>Dapagliflozin</td>
<td>17 150</td>
<td>MACE</td>
<td>completion in 2019</td>
<td></td>
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<tr>
<td>Ertugliflozin CVOT</td>
<td>NCT01986881</td>
<td>Ertugliflozin</td>
<td>3900</td>
<td>MACE</td>
<td>completion in 2021</td>
<td></td>
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</tbody>
</table>

*Hazard ratio (95% confidence interval)

Based on data from references 55-58 and 67-69.

References
Cardiovascular safety of oral antidiabetic drugs – Simpson


Keywords: adverse reactions; cardiovascular disease; hypoglycemic agent; risk assessment; type 2 diabetes

Tolérance cardio-vasculaire des antidiabétiques oraux

Le risque de développer une maladie cardio-vasculaire est significativement plus élevé chez les diabétiques de type 2 que dans la population générale, ce qui est une cause importante de morbidité et de mortalité. Les effets bénéfiques de l’abaissement de la glycémie grâce aux antidiabétiques oraux sont bien établis, mais certains de ces médicaments sont associés à un risque accru d’événements cardio-vasculaires. L’exemple le plus connu est peut-être l’association entre la rosiglitazone et le risque d’insuffisance cardiaque et d’infarctus du myocarde. Les sulfonlurylurés posent également des questions de tolérance cardio-vasculaire. Notre compréhension de la tolérance cardio-vasculaire des nouvelles classes d’antidiabétiques oraux (inhibiteurs de la dipeptidyl peptidase-4 et inhibiteurs du cotransporteur sodium-glucose de type 2) est en train d’évoluer. À l’inverse, la metformine et l’acarbose ne semblent pas entraîner d’événements cardio-vasculaires indésirables. Suite à ces questions, la Food and Drug Administration aux États-Unis a demandé des études de tolérance cardio-vasculaire dans le cadre des processus d’approbation réglementaire pour les nouveaux antidiabétiques. De plus, la tolérance cardio-vasculaire des antidiabétiques a fait l’objet de nombreuses études observationnelles, d’essais contrôlés randomisés et de méta-analyses. Cet article passe en revue les problèmes et les données actuels liés à la tolérance cardio-vasculaire de chaque classe d’antidiabétique oral. Une bonne compréhension du risque cardio-vasculaire éventuel associé à ces médicaments aidera médecins et patients dans les décisions thérapeutiques pour la prise en charge du diabète de type 2.
Beyond metformin: selecting a second therapy

by T. M. E. Davis, Australia

Metformin is widely accepted first-line therapy for type 2 diabetes but glycemic progression often means that addition of a second drug becomes necessary to maintain adequate blood glucose control. The choice of second-line agents comprises oral therapies (sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, dipeptidyl-peptidase 4 (DPP-4) inhibitors, or sodium glucose cotransporter 2 (SGLT2) inhibitors) or injectable therapies (glucagon-like peptide 1 (GLP-1) agonists or insulin). In systematic reviews and meta-analyses of available data, there is little glycemic difference between candidate oral therapies, which means that class- and/or drug-specific tolerability and potential other beneficial and adverse effects will be the main drivers of utilization.

Metformin is conventionally recommended as first-line pharmacotherapy for type 2 diabetes. This is mainly because it is effective in improving glycemia without associated weight gain or hypoglycemia, properties that have been evident from a wide range of clinical studies and extensive use in usual care over many decades. There is some evidence, largely from the landmark UKPDS study (UK Prospective Diabetes Study), that metformin may be cardioprotective independent of its blood glucose-lowering effects, but this potential benefit has been debated in the light of more recent data. Apart from gastrointestinal symptoms, which can be reduced through use of extended-release formulations, it is well tolerated. Although not universally accepted, its most serious adverse effect is lactic acidosis, which is rare and which usually occurs in the presence of other risk factors.

The choice of second-line therapy after metformin in type 2 diabetes should be informed by an objective evaluation of efficacy and adverse effects, attributes that will need to be assessed together with patient preferences and the economic limitations of the health care system. Based on systematic reviews and meta-analyses, there is not much glycemic difference between candidate oral therapies, which means that tolerability and potential adverse and other effects will be the main drivers of utilization.
Beyond metformin: selecting a second therapy – Davis

In patients who cannot tolerate metformin, in whom it is contraindicated or not recommended, or in those who do not achieve glycemic targets despite appropriate doses, a second oral agent is indicated. The choice of blood glucose-lowering therapy in this situation has broadened in recent years with the emergence of the incretin-based therapies (comprising inhibitors of dipeptidyl-peptidase 4 [DPP-4], and the glucagon-like peptide 1 [GLP-1] agonists) as well as inhibitors of the sodium glucose cotransporter 2 (SGLT2). These relatively new therapies can be considered as second-line agents alongside the more established drugs, which include sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, and insulin. The choice of drug in this situation will depend mainly on relative efficacy, adverse effects, and cost (see Table). 7

In addition, potential benefits beyond blood glucose-lowering should be considered. The merits of each of these second-line therapies will be considered in this review.

Sulfonylureas

The drugs in this class (glibenclamide, gimepiride, glipizide, and gliclazide), as well as the shorter-acting meglitinides (repaglinide and nateglinide), bind to the sulfonylurea receptor on the membrane of the pancreatic \( \beta \)-cells to stimulate endogenous insulin production, a mechanism which is distinct from—and thus complementary to—the blood glucose-lowering effects of metformin.

**Glycemic efficacy**

The sulfonylurea drugs have similar blood glucose-lowering effects to metformin and reduce glycated hemoglobin (HbA1c) from an average baseline of around 8.0% (64 mmol/mol) by a mean or median of 0.8%-1.0% (9-11 mmol/mol) when added to metformin in dual combination therapy. 8,9 However, their glycemic efficacy depends on the time after initiation in monotherapy studies, with a relatively potent effect in the first 3 to 6 months which wanes progressively over the next 1 to 2 years.10 Given that type 2 diabetes is characterized by continuing loss of \( \beta \)-cell function, this time-dependent therapeutic failure may be more pronounced when sulfonylureas are combined with metformin since insulin secretory capacity is likely to be less in a patient who has progressed to two blood glucose-lowering therapies rather than one. This has yet to be demonstrated in comparative studies.

The limited durability of sulfonylureas has been attributed to \( \beta \)-cell toxicity and accelerated apoptosis in short-term animal and in vitro studies,11 but rapid weight reduction through bariatric surgery12 or very low energy diets13 in patients with type 2 diabetes on treatments including sulfonylurea-met-
formin can resuscitate β-cell function. This suggests that sulfonylureas are not directly toxic to β cells when given in conventional pharmacological doses. Sulfonylureas increase post-prandial glucagon secretion,14 and this may underlie or contribute to secondary failure as enhanced α-cell function starts to predominate over progressive β-cell loss.

Adverse effects

The sulfonylureas are generally well tolerated. However, consistent with their glucose-independent β-cell stimulatory effects, they are the most likely oral blood glucose-lowering agent to cause hypoglycemia. This includes at least a fourfold increased risk when combined with metformin.6,9 There are, however, within-class differences in hypoglycemia risk. The longer-acting sulfonylureas with active renally excreted metabolites such as glibenclamide and glimepiride are more likely to cause hypoglycemia, while gliclazide is the least likely.10 A pertinent example is provided by one study in which the glycemic efficacy of glimepiride and gliclazide were compared and in which the majority of patients were taking metformin monotherapy at baseline.11 The risk of hypoglycemia was significantly lower in gliclazide-treated patients to that seen in the glimepiride group for a similar reduction in HbA1C. Weight gain with insulin secretagogues is moderate and, in the case of the addition of a sulfonylurea to metformin therapy, typically 1 to 3 kg.6,9

Chronic complications

There are few micro- or macrovascular outcome data relating to the relative effect of combining metformin with a sulfonylurea. Perhaps one of the most controversial relevant studies was the UKPDS study, in which diabetes-related deaths were almost doubled in overweight patients taking metformin and sulfonylurea therapy compared with those on a sulfonylurea alone.7 This was attributed to the play of chance since the mortality in the sulfonylurea monotherapy group was unusually low. In addition, post-study monitoring showed that this finding became nonsignificant with accrual of a greater number of events in contrast to the continued significant benefits for intensively treated UKPDS patients as a whole.17 No increased cardiovascular disease (CVD) or mortality risk for sulfonylurea-metformin-treated patients has been found in other studies including observational data from representative community-based samples.18 In pooled analyses, sulfonylurea therapy with or without metformin does not appear to increase the risk of CVD events compared with a variety of comparator regimens, while gliclazide appears to have the safest CVD profile within the class.19

Thiazolidinediones

The thiazolidinediones or glitazones (pioglitazone and rosiglitazone) act to improve tissue insulin sensitivity through activation of the peroxisome proliferator–activated receptor gamma nuclear receptor and thus also have complementary blood glucose-lowering effects to those of metformin.

Glycemic efficacy

Compared with metformin monotherapy, the addition of a glitazone reduces the HbA1C from an average baseline of around 8.0% (64 mmol/mol) by a mean or median of 0.7%-0.8% (8-9 mmol/mol).6,9 The glycemic durability of the glitazones is significantly greater than both sulfonylurea and metformin in monotherapy studies.10 Although it is likely that a metformin–glitazone combination will retain its efficacy for longer than metformin–sulfonylurea as a result, there are no prospective studies that have examined this hypothesis.20

Adverse effects

The addition of glitazone therapy to metformin does not increase the risk of hypoglycemia.6,9 This reflects the insulin sensitizing properties of this class. Weight gain resulting from the addition of a glitazone to background metformin is a mean or median of 2 to 4 kg in intervention studies,6,9 but real-life experience suggests that this figure may be greater.21 In contrast to sulfonylurea therapy, in which enhanced insulin secretion underlies weight gain, the glitazones stimulate adipogenesis but they also redistribute fat away from visceral depots.22 This could theoretically contribute to a reduction in CVD risk.

Chronic complications

As with sulfonylureas, there are few outcome data relating to the relative effect of combining metformin with a glitazone.6,9 The RECORD trial (Rosiglitazone Evaluated for Cardiovascular Outcomes in oRal agent combination therapy for type 2 Diabetes) compared rosiglitazone-metformin with sulfonylurea-metformin therapy and did not find that the two regimens differed in the number of major adverse cardiovascular events (MACE) outcomes (nonfatal myocardial infarction, nonfatal stroke, and CVD death),23 a reassuring result given the controversy surrounding rosiglitazone engendered by a meta-analysis of available CVD and mortality data in 2007.24 The PROactive trial (PROspective pioglitAzone Clinical Trial In macroVascular Events) showed that the addition of pioglitazone to usual therapy did not significantly reduce a primary end point that included MACE components,25 but a separate comparative analysis of the 10% of patients on metformin alone at study entry has not been reported.

There are no data assessing whether other recognized adverse effects of glitazones, including fluid retention and fractures,10 are increased or reduced in patients taking pioglitazone or rosiglitazone in combination with metformin. Concerns regarding an association between pioglitazone and bladder cancer initially raised by PROactive25 have been attenuated by recent population-level data.26

Alpha-glucosidase inhibitors

The drugs in this class (acarbose, miglitol, and voglibose) slow carbohydrate absorption through inhibition of alpha glucosidase, and they increase circulating GLP-1 concentrations.27 Their main effect is on postprandial glycermia.
Glycemic efficacy
Compared with metformin monotherapy, the addition of an alpha-glucosidase inhibitor reduces the HbA1c by a median of 0.7% (8 mmol/mol) from a meta-analysis of available data. However, a recent study has shown that acarbose significantly attenuates the bioavailability of metformin when they are co-administered, but the authors concluded that the accumulated evidence of the glycemic efficacy of this combination implied that this interaction was not clinically significant.

Adverse effects
The addition of an alpha-glucosidase inhibitor to metformin does not increase the risk of hypoglycemia or alter body weight. Although both drugs have the potential to cause gastrointestinal side effects such as nausea, vomiting, diarrhea, and abdominal pain, their combination does not appear to increase the incidence of these symptoms to a greater degree than monotherapy with either drug. Nevertheless, at least some of these studies were carried out in samples of Asian patients and there is evidence that Asian racial groups tolerate alpha-glucosidase inhibitors better than White Caucasians. In the UKPDS, for example, only 39% of patients remained on acarbose therapy after 3 years versus 58% on placebo.

Chronic complications
There are no randomized trials that have examined whether the addition of an alpha-glucosidase inhibitor to metformin therapy influences the risk of chronic complications of diabetes. However, in the light of suggestions that acarbose is associated with CVD benefit in observational studies and in meta-analyses of data from intervention studies in which CVD events were not the primary outcome, a large-scale placebo-controlled trial of acarbose in Asian patients with CVD and prediabetes has been started, but combination with metformin will only occur when the latter drug is prescribed in cases of progression to type 2 diabetes.

DPP-4 inhibitors
The drugs in this class (sitagliptin, vildaglitipin, saxagliptin, linagliptin, and alogliptin) inhibit the DPP-4 enzyme that mediates physiological degradation of the incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), thus promoting insulin secretion and inhibiting inappropriate glucagon secretion. There is evidence that the effect of a DPP-4 inhibitor given with metformin on circulating active GLP-1 concentrations is additive, supporting their therapeutic coadministration.

Glycemic efficacy
The DPP-4 inhibitors reduce HbA1c from an average baseline of around 8.0% (64 mmol/mol) by a median of 0.7%-0.8% (8-9 mmol/mol) when added to metformin in dual combination therapy. An analysis of pooled data suggests that there are no differences in glycemic efficacy between drugs in this class when combined with metformin, apart from evidence that patients on alogliptin plus metformin achieve an HbA1c target <7.0% (53 mmol/mol) more frequently than those treated with saxagliptin plus metformin.

Adverse effects
The DPP-4 inhibitors are well tolerated, including when given with metformin, with neutral effects on hypoglycemia risk and body weight. In the cardiovascular safety trials involving alogliptin, saxagliptin, and sitagliptin, in which at least two-thirds of patients were taking background metformin therapy, there were nonsignificant excesses of cases of acute pancreatitis in each active arm, which supports the warning of this potential adverse event that is already included in the product information of all the DPP-4 inhibitors. There was, however, no evidence of an increased risk of pancreatic cancer, albeit from a follow-up period (up to 3 years) that is too short to rule out carcinogenicity.

Chronic complications
The primary end point in the three DPP-4 inhibitor cardiovascular safety trials that have been reported to date was MACE with or without unstable angina. The cumulative frequencies of these events in the active versus placebo arms in these trials were effectively co-linear, which—given how commonly metformin was also prescribed—suggests that DPP-4 inhibitor-metformin combination therapy has a neutral short-term effect on CVD. There are, however, apparent between-drug differences in other complications, with saxagliptin and perhaps alogliptin, but not sitagliptin, associated with an increased risk of heart failure. On the other hand, saxagliptin appears to be beneficial for albuminuria but there was no such effect in the case of sitagliptin.

GLP-1 agonists
These drugs (including exenatide, lixisenatide, exenatide extended release, lixaglutide, and semaglutide) bind to the GLP-1 receptor and, as with DPP-4 inhibitors, promote insulin secretion and inhibit inappropriate glucagon secretion. However, they also suppress appetite and, especially in the case of the shorter-acting drugs in the class (exenatide and lixisenatide), delay gastric emptying.

Glycemic efficacy
The GLP-1 agonists reduce HbA1c from an average baseline of around 8.0% (64 mmol/mol) by a median of 0.7%-0.8% (8-9 mmol/mol) when added to metformin in dual combination therapy. However, there may be within-class differences. In a comparison of exenatide and lixaglutide on a background of metformin with or without sulfonylurea therapy in most cases, patients treated with the longer-acting lixaglutide had a 0.3% (3 mmol/mol) lower mean HbA1c. In addition, GLP-1 agonists such as exenatide and lixisenatide, which share only approximately 50% homology with human GLP-1, are potentially antigenic; this may attenuate their glycemic efficacy over time.
◆ Adverse effects
The GLP-1 agonists are relatively commonly associated with nausea and vomiting (up to 50% in some trials46), especially with the shorter-acting agents,43 but these symptoms can resolve with continued use. There are no published formal analyses of whether their use with metformin increases the risk of gastrointestinal side effects but, despite the fact that they are injected therapies, overall treatment satisfaction appears at least as good with this combination as with GLP-1 agonist-sulfonylurea treatment.42 This latter finding could reflect the beneficial psychological effects of weight loss (a median of around 2 kg in pooled analyses of GLP-1 agonist studies involving a majority of patients on background metformin), without an increase in hypoglycemia.9 As with DPP-4 inhibitors, there is evidence from case reports and intervention trials published to date of an excess of pancreatitis, which has been a low frequency adverse event.42,43 Whether their combination with metformin influences this risk is unknown.

◆ Chronic complications
The results of only one CVD safety trial, that involving lixisenatide,44 have been reported and there was a neutral effect on MACE outcomes in patients who were mostly treated with background metformin alone or in combination with other oral agents (American Diabetes Association Scientific Sessions, Boston, June 2015). There are nonglycemic factors, which suggest that the GLP-1 agonists might prevent (through lower blood pressure and more advantageous serum lipid profiles) or contribute to (through increased resting pulse rate) CVD,42,43 but whether these are influenced by metformin co-administration is unknown.

SGLT2 inhibitors
The drugs in this class (dapagliflozin, canagliflozin, and empagliflozin) increase urinary glucose excretion through inhibiting its reabsorption from the proximal renal tubule, a mode of action that is independent of that of metformin.

◆ Glycemic efficacy
The SGLT2 inhibitors reduce HbA1c from an average baseline of around 8.0% (64 mmol/mol) by a mean of 0.5%-0.9% (6-10 mmol/mol) when added to metformin in dual combination therapy.45 There is evidence from a study in healthy volunteers that canagliflozin may be the most active agent in the class because, in addition to comparable SGLT2 inhibitory activity, it has greater activity against SGLT1 in the gastrointestinal tract.42 Whether coadministered metformin influences this apparent difference in the context of type 2 diabetes is unknown.

◆ Adverse effects
The SGLT2 inhibitors are associated with a higher incidence of genitourinary infections and some symptoms related to mild dehydration than comparator blood glucose-lowering therapies regardless of whether they are used alone or in combination with other blood glucose-lowering therapies.46 They do not increase the risk of hypoglycemia, and cause 2 to 4 kg of weight loss, mainly during the first 3 to 6 months of use, including when partnered with metformin.46 A recent development has been case reports of ketoacidosis, which could reflect the proactive reduction in insulin doses, increased glucagon secretion, and reduced renal clearance of ketone bodies associated with SGLT2 inhibitor treatment,51 but metformin does not appear to be influential.46

◆ Chronic complications
There are randomized, placebo-controlled phase 4 CVD safety trials in progress in the case of each of the agents in this class and that involving empagliflozin has recently been completed.49 There were significant 14%, 38%, and 36% reductions in MACE, cardiovascular death, and hospitalization for heart failure, respectively, in patients allocated to empagliflozin. Almost three-quarters of patients were taking metformin at baseline but this was monotherapy in a relatively small proportion. Nevertheless, the overall results appear consistent with statistical modeling suggesting that the overall favorable effects of SGLT2 inhibitors on risk factors such as hypertension should have benefits for the chronic complications of diabetes managed conventionally with metformin as first-line oral therapy.46

Insulin
Insulin therapy is acknowledged as a valid second-line therapy after metformin, especially in patients with relatively poor glycemic control.1

◆ Glycemic efficacy
Basal and biphasic insulin therapy reduce HbA1c in metformin-treated patients by medians of 0.8% (9 mmol/mol) and 1.0% (11 mmol/mol),2 but whether there is a clear difference in glycemic efficacy between these two insulin regimens is unclear.8

◆ Adverse effects
As with insulin in any therapeutic context, the main limitation is hypoglycemia, which is increased by medians of 5.2 and 11.0 times that associated with metformin alone with basal and biphasic insulin, respectively,9 the greatest increases of any second-line therapy. Weight gain is also a concern, with median increases of 1.6 and 3.0 kg, respectively.9

◆ Chronic complications
There are no published prospective outcome studies specifically assessing the effects of the addition of insulin to metformin on chronic complications of diabetes.

Discussion
The choice of second-line therapy after metformin in type 2 diabetes should be informed by an objective evaluation of efficacy and adverse effects, attributes that will always need to
be assessed together with patient preferences and the economic limitations of the health care system. Based on systematic reviews and meta-analyses,\textsuperscript{8,9} there is not much glycemically significant difference between candidate oral therapies, which means that tolerability, and potential other beneficial or adverse effects, will be the main drivers of utilization in this situation. Considering pooled analyses\textsuperscript{9} and structured comparative studies involving a range of expected comparator drugs (one example being liraglutide\textsuperscript{45}), injectable therapies appear more likely to achieve glycemic targets than oral medications, with GLP-1 agonists having advantages over insulin in relation to hypoglycemia and body weight effects. Newer agents are expensive, however, especially since large-scale CVD safety trials are now done almost routinely as part of the development of blood glucose-lowering therapies. In addition, and in light of the rosiglitazone experience,\textsuperscript{24} prescribers may adopt a conservative approach and wait for sufficient reassuring phase 4 adverse effect data to justify their use as part of usual care. The recent publication of positive cardiovascular findings for empagliflozin\textsuperscript{49} are likely to shift the choice of second-line therapy towards SGLT2 inhibitors. However, further trials of agents in this class and of the more potent GLP-1 agonists are in progress or completing, and their results may also be influential in modifying the therapeutic algorithm.

The main aspects of a position statement published by members of the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) that relate to second-line therapy are shown in the table.\textsuperscript{1,7} The conclusions that DPP-4 inhibitors, SGLT2 inhibitors, and alpha-glucosidase inhibitors have inferior relative glycemic efficacy when used in combination with metformin do not appear consistent with the available data.\textsuperscript{5,6,46} Nevertheless, the suggested framework for assessing treatment options is valid. Although phase 4 CVD safety trial data are valuable for the range of information they provide, their pragmatic design (addition of active therapy or placebo to usual care) makes it difficult to dissect out the benefits and risks of particular treatment combinations, including with metformin alone as baseline therapy. Although the SGLT2 inhibitor class is not represented, the GRADE study (Glycemia Reduction Approaches in Diabetes: a comparative Effectiveness study)\textsuperscript{54} will hopefully provide much-needed comparative data on the long-term glycemic effectiveness of other second-line therapies to inform clinical use. GRADE may also add to the adverse effect databases of the individual therapies.

Adherence to treatment is also an issue that is not captured by intervention studies, which are designed to ensure that the medications are taken exactly as prescribed so that true differences in efficacy and side effects are captured. As pointed out in the ADA/EASD position statement, drugs such as the alpha-glucosidase inhibitors which have to be taken at least twice daily may not be associated with as good compliance as once daily (or even once weekly in the case of exenatide extended release and semaglutide) medications, with adverse effects on glycemic control.\textsuperscript{53}

Although phase 4 CVD safety trial data are valuable for the range of information they provide, their pragmatic design (addition of active therapy or placebo to usual care) makes it difficult to dissect out the benefits and risks of particular treatment combinations, including with metformin alone as baseline therapy. Although the SGLT2 inhibitor class is not represented, the GRADE study (Glycemia Reduction Approaches in Diabetes: a comparative Effectiveness study)\textsuperscript{54} will hopefully provide much-needed comparative data on the long-term glycemic effectiveness of other second-line therapies to inform clinical use. GRADE may also add to the adverse effect data bases of the individual therapies.

References

Keywords: glycemic efficacy; metformin; second-line therapy; tolerability; type 2 diabetes
CHOISIR UN TRAITEMENT DE SECONDE LIGNE À ASSOCIER À LA METFORMINE

La metformine est un traitement de première ligne largement accepté pour le diabète de type 2, mais la progression glycémique entraîne souvent la nécessité d’un traitement supplémentaire de seconde ligne pour maintenir un contrôle glycémique suffisant. Les traitements de seconde ligne comprennent à la fois des médicaments par voie orale (sulfonlurées, thiazolidinediones, alpha-glucosidase, inhibiteurs de DPP-4 [dipeptidyl peptidase-4] ou inhibiteurs de SGLT2 [cotransporteur sodium-glucose de type 2]) et des médicaments injectables (agonistes du GLP-1 [glucagon-like peptide 1] ou l’insuline). La différence au niveau glycémique entre les médicaments oraux est infime dans les méta-analyses et les analyses systématiques des données disponibles. Ce qui signifie que les données spécifiques à un médicament et/ou spécifiques à la classe de médicaments auquel il appartient en matière de tolérance et d’effets bénéfiques ou indésirables potentiels seront les principaux motifs justifiant son utilisation dans cette situation. Les traitements injectables semblent être mieux capables d’atteindre les cibles glycémiques que les traitements oraux, les avantages des agonistes du GLP-1 sur l’insuline étant d’induire moins d’hypoglycémiées et de permettre une perte plutôt qu’un gain de poids. La préférence du patient, le coût (les exigences pour les études de tolérance cardio-vasculaires de phase 4 peuvent l’alourdir de façon significative en cas de nouveaux traitements) et l’adhésion du patient (meilleure avec une prise quotidienne ou hebdomadaire qu’avec plusieurs prises par jour) sont d’autres considérations entrant en jeu dans le choix d’un traitement de seconde ligne. De plus en plus de données sur l’efficacité, la tolérance et les événements indésirables des inhibiteurs de DPP-4 et du SGLT2 et des agonistes du GLP-1 sont générées par les études de tolérance cardio-vasculaires de phase 4. D’autres études d’efficacité comparant les médicaments de seconde ligne sont en cours. De fait, les récents résultats cardio-vasculaires positifs de la première étude de phase 4 d’un inhibiteur du SGLT2 pourraient avoir un effet important sur le choix d’un co-médicament à utiliser avec la metformine.
In ADVANCE, clear benefits of intensive glucose control were primarily due to reductions in new or worsening nephropathy, driven by reductions in progression of albuminuria and the “hard” clinical outcome of end-stage kidney disease requiring renal replacement therapy. In ADVANCE-ON, persisting benefits for this “hard” clinical outcome were observed. If persistence of in-trial benefits during the posttrial period constitutes a metabolic memory or legacy effect, then we had this in ADVANCE-ON for end-stage kidney disease.

Posttrial follow-up studies of patients with diabetes have previously reported long-term beneficial effects of earlier periods of intensive glucose control on a range of outcomes, including mortality and macrovascular events.1,2 The Epidemiology of Diabetes Intervention and Complications (EDIC) study extension of the Diabetes Control and Complications Trial (DCCT) in young patients with type 1 diabetes with no history of cardiovascular disease, hypertension, or hypercholesterolemia reported a lower risk of macrovascular events, as well as sustained benefit for microvascular complications beyond the period of randomized treatment.1 The postintervention follow-up of the United Kingdom Prospective Diabetes Study (UKPDS) also reported long-term beneficial effects of intensive glucose control in patients with newly diagnosed type 2 diabetes.3 In patients formerly assigned to intensive therapy, the reduced risk of microvascular events was maintained and previously nonsignificant estimates of effect on death and myocardial infarction became significant compared with patients on conventional therapy, with extended follow-
up. These long-term benefits were ascribed to a metabolic memory or legacy effect of prior intensive glucose lowering. The ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation) trial assessed the effects of intensive glucose control versus standard glucose control in a broad cross-section of patients with type 2 diabetes. Intensive glucose control was associated with a reduction in risk of the composite primary outcome of major macrovascular and microvascular events, primarily due to a clear reduction in new or worsening nephropathy. This included a reduction in the need for renal replacement therapy. The trial identified no clear protective or harmful effects of intensive glucose control on all-cause death or major macrovascular events. The posttrial follow-up of ADVANCE, ADVANCE-ON (Observational study), investigated whether the in-trial intensive glucose control produced long-term benefits after completion of randomized treatment.

**Methods**

ADVANCE-ON was a posttrial follow-up study of all surviving ADVANCE patients. The recruitment of patients, study design, and detailed methods for the ADVANCE trial have previously been published. In brief, 11,140 individuals with type 2 diabetes aged 55 years or older with at least one additional risk factor for cardiovascular disease were enrolled from 215 centers in 20 countries between 2001 and 2003. Patients were randomly assigned to: (i) a gliclazide modified release (MR)-based intensive glucose control regimen, aiming for a glycated hemoglobin (HbA1c) level of 6.5% or lower, or to standard glucose control based on local guidelines of participating countries; and (ii) to a single-pill (fixed-dose) combination of perindopril and indapamide (4 mg/1.25 mg) or matching placebo, after a 6-week active run-in period.

The last ADVANCE trial visits for the blood glucose control comparison were completed in January 2008, after a median follow-up period of 5.0 years. At this time, patients ceased the randomized interventions and returned to the usual care of their treating physician.

**Posttrial follow-up and assessments**

All local ADVANCE trial sites were invited to participate in ADVANCE-ON and 172 of 215 (80%) agreed. In April 2010, annual posttrial visits commenced. A random subset of 2000 patients, balanced across regions and across the prior randomized treatment arms, was also invited to undergo assessment of HbA1c, fasting blood glucose, blood pressure, weight, serum creatinine, and urinary albumin:creatinine ratio at the first posttrial visit.

**Study outcomes**

The two prespecified primary outcomes for ADVANCE-ON were death from any cause and major macrovascular events (a composite of nonfatal myocardial infarction, nonfatal stroke, or death from any cardiovascular cause). The major microvascular event outcome, as defined in the ADVANCE trial, could not be evaluated in ADVANCE-ON as assessment of serum creatinine and albuminuria were only performed in a subgroup of participants. Consequently, the prespecified secondary outcome for ADVANCE-ON was major clinical microvascular events, defined as a composite of requirement for renal replacement therapy, death from renal disease, and severe diabetes-related eye disease (requirement for retinal photocoagulation or diabetes-related blindness in either eye). Other secondary outcomes included the separate components of this outcome and death from any cardiovascular cause, fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, and major hypoglycemia.

**Results**

As reported, 8494 patients (84%) entered posttrial follow-up and 5131 completed a visit during the final year of the study. The median in-trial, posttrial, and total follow-ups were 5.0 years, 5.4 years, and 9.9 years, respectively. The first posttrial visit occurred a median of 2.9 years after the final ADVANCE trial visit.  

**Patient characteristics**

The prerandomization characteristics of the ADVANCE trial patients who were enrolled in ADVANCE-ON were broadly similar, according to original treatment assignment, to those of the entire ADVANCE trial cohort. A slightly lower prevalence of established vascular disease in the ADVANCE-ON cohort was consistent with a healthy survivor effect.

**Treatment patterns**

Posttrial use of insulin therapy initially decreased, but then increased in the intensive group and steadily increased in the standard group. In contrast, posttrial use of gliclazide MR decreased in the intensive group, whilst the use of other sulfonylureas decreased in the standard group. Use of other glucose-lowering therapies, such as gliptins and glucagon-like peptide 1 analogues, increased in both groups. There were no

**Selected abbreviations and acronyms**

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<th>Abbreviation</th>
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<tr>
<td>ADVANCE</td>
<td>Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation</td>
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<td>ADVANCE-ON</td>
<td>Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation—Observational study</td>
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<tr>
<td>DCCT</td>
<td>Diabetes Control and Complications Trial</td>
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<td>EDIC</td>
<td>Epidemiology of Diabetes Intervention and Complications</td>
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<td>glycated hemoglobin</td>
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<td>UKPDS</td>
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substantive posttrial differences between the original randomized groups in the use of metformin, thiazolidinediones, and α-glucosidase inhibitors.

**HbA1c differences**

The mean in-trial difference in HbA1c (0.67%; 95% confidence interval [CI] 0.64% to 0.70%) at the end of randomized therapy was lost by the first posttrial visit (0.08%; 95% CI, -0.07% to 0.22%), with a rise in HbA1c in the intensive control group approaching that observed in the standard control group. HbA1c levels in the two groups remained similar at the conclusion of posttrial follow-up (7.2% vs 7.4%).

**Primary and secondary outcomes**

Consistent with in-trial findings, there were no cumulative benefits of intensive glucose control for either death from any cause or major macrovascular events (Figure 1). There was also no evidence that the cumulative effects on death from any cause varied between the patient subgroups studied (all P>0.1). In addition, there were no cumulative benefits for major clinical microvascular events or severe diabetes-related eye disease considered separately. However, there was a highly significant cumulative benefit across the overall in-trial and posttrial period for end-stage kidney disease (hazard ratio [HR] for requirement for renal replacement therapy, 0.54; 95% CI, 0.34-0.85) (Figure 1). No beneficial effects emerged during the posttrial period for any other secondary outcome. There was no interaction between the effects of glucose control and BP lowering for any primary or secondary outcome (all P for interaction >0.1). During posttrial follow-up, the incidence of major hypoglycemia was evenly distributed across groups (295 events in the intensive group and 292 in the standard group).

**Commentary**

After a total of 10 years of in-trial and posttrial follow up of the ADVANCE cohort, no long-term benefits for mortality or macrovascular events were observed. However, the large benefit for end-stage kidney disease observed in-trial was sustained. In ADVANCE, clear benefits of intensive glucose control were primarily due to reductions in new or worsening nephropathy, driven by reductions in progression of albuminuria and the "hard" clinical outcome of end-stage kidney disease requir-

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**Figure 1.** Cumulative incidence of death from any cause, major macrovascular events, and end-stage kidney disease, according to glucose-control group.

This figure shows the percentage of patients who had events at any time after randomized treatment was started, according to glucose-control group (intensive or standard). Hazard ratios (intensive versus standard) and P values are shown for the 10-year period from the start of randomized treatment to the end of the posttrial follow-up. No significant difference between the intensive and standard glucose-control groups was found for death from any cause (panel A) or major macrovascular events (panel B), but a significant difference in end-stage kidney disease was observed (panel C). For the reader’s benefit, the panel C inset shows data on an enlarged y axis.

ing renal replacement therapy. In ADVANCE-ON, persisting benefits for this "hard" clinical outcome were observed. If persistence of in-trial benefits during the posttrial period constitutes a metabolic memory or legacy effect, then we had this in ADVANCE-ON for end-stage kidney disease.

Our findings differ from the DCCT-EDIC and UKPDS posttrial follow-up studies.1,2 Both of these trials reported the emergence of long-term beneficial effects of earlier periods of intensive glucose control on major macrovascular events and/or mortality.1,2 It is possible that there were physiological differences in response to glucose lowering across the trial populations in DCCT-EDIC, UKPDS, and ADVANCE. First, the younger patients with type 1 diabetes (DCCT-EDIC)1 or newly diagnosed type 2 diabetes (UKPDS)2 may have been more likely to achieve long-term benefits from glucose lowering than older patients with established disease included in ADVANCE. Second, there were differences between the studies in terms of in-trial exposure to HbA1c, which differed by only 0.7% over 5 years in ADVANCE, but was much larger in the DCCT (∆HbA1c was 2.0% over a mean follow-up of 6.5 years) and slightly larger in the UKPDS (∆HbA1c was 0.9% over a median follow-up of 10 years).1,2 Baseline HbA1c levels of patients were also much higher in the DCCT and UKPDS (both >8.5%) than in ADVANCE (7.5%).1,2 Third, more widespread use of better background preventive therapy in ADVANCE may have masked any long-term beneficial effects on mortality and cardiovascular events.

**Conclusion**

Intensive glucose control is important for preventing serious renal complications and does not cause harm, i.e., does not increase risk of mortality or cardiovascular events, in people with longstanding type 2 diabetes.

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**References**


**Keywords:** ADVANCE-ON; end-stage kidney disease; gliclazide; intensive glucose control; legacy effect; metabolic memory; type 2 diabetes

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**EFFETS À LONG TERME D’UN CONTRÔLE GLYCEMIQUE INTENSIF DANS LE DIABÈTE DE TYPE 2 DANS L’ÉTUDE ADVANCE-ON**

L’étude ADVANCE (Action in Diabetes and Vascular disease : PreterAx and Diamicron MR Controlled Evaluation), a montré qu’un contrôle glycémique intensif (HbA1c ciblée ≤ 6,5 %) diminue le risque de néphropathie comparé au contrôle glycémique standard chez les diabétiques de type 2. L’étude de suivi ADVANCE-ON a analysé le maintien des effets d’ADVANCE ou l’apparition de nouveaux bénéfices à long terme pour les principaux résultats. Les critères primaires étaient la mortalité toutes causes et les événements macrovasculaires majeurs. Les critères secondaires comprenaient les événements cliniques microvasculaires majeurs et la nécessité d’un traitement rénal de substitution. Sur 11 140 patients initialement randomisés, 8 494 ont été suivis en post-étude pendant une durée médiane de 5,4 ans. Les différences intra-étude des taux de HbA1c entre les groupes de traitement ont disparu lors de la première visite de post-randomisation après 2,9 ans. Aucune diminution n’a été observée en ce qui concerne le risque cumulatif de mortalité toutes causes (RR rapport de risques du contrôle intensif versus standard, 1 ; IC 95 % : 0,92-1,08), les événements macrovasculaires majeurs (RR 1 ; IC 95 % : 0,92-1,08) ou les événements microvasculaires majeurs (RR 0,92 ; IC 95 % : 0,8-1,05). En revanche, le risque cumulatif d’insuffisance rénale terminale (IRT) a significativement diminué dans le groupe intensif (RR 0,54 ; IC 95 % : 0,34-0,85). Le suivi post-étude n’a pas montré d’effets bénéfiques des différences intra-études du contrôle glycémique sur la mortalité à long terme ou les événements macrovasculaires majeurs. Par contre, les bénéfices avérés significatifs intra-étude sur l’IRT soulignent l’importance du contrôle glycémique pour la protection rénale.
Diabetic kidney disease: natural history and pathophysiology

by P. Fioretto, Italy

Diabetic nephropathy is the most common cause of end-stage renal disease worldwide. Blood glucose and blood pressure control reduce the risk of developing this complication; however, once diabetic nephropathy is established, it is only possible to slow its progression. In the last few decades, there has been a significant reduction in all chronic diabetic complications except for diabetic nephropathy. Thus, despite guidelines recommending screening and nephroprotective care, the risk of diabetic nephropathy is not decreasing among patients with type 2 diabetes. The renal lesions underlying renal dysfunction differ between type 1 and type 2 diabetes, although the clinical manifestations of diabetic nephropathy—proteinuria, decreased glomerular filtration rate, and increased blood pressure—are similar. Indeed, in type 1 diabetes, despite the presence of tubular, interstitial, and arteriolar lesions, the most important structural changes involve the glomerulus. This contrasts with type 2 diabetes, in which a substantial proportion of patients have normal glomerular structure with or without tubulointerstitial and arteriolar abnormalities, despite the presence of microalbuminuria or proteinuria. The clinical manifestations of diabetic nephropathy are strongly related to structural changes, especially the degree of mesangial expansion in both type 1 and type 2 diabetes. Changes in the structure and number of podocytes may also be involved in the progression of diabetic nephropathy, especially in type 2 diabetes.

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Diabetes mellitus is a worldwide, growing public health problem associated with high risks of severe microvascular and macrovascular complications. The number of patients with diabetes mellitus, mostly type 2 diabetes, is expected to increase globally from an estimated 382 million (8.3% of the adult population) in 2013 to 592 million (10.0%) by 2035.1 Diabetic nephropathy is a devastating complication of diabetes and is a major cause of illness and death. The excess mortality of diabetes occurs mainly in proteinuric diabetic patients and is a result not only of end-stage renal disease (ESRD), but also of cardiovascular disease, with the latter being a particularly common cause in type 2 diabetic patients.2 Diabetic nephropathy is the single most common cause of ESRD in Europe, Japan, and the United States, with diabetic patients accounting for 25% to 45% of all patients enrolled in ESRD programs.3,4 The rate of increase of ESRD in diabetes has been much faster than that in other diseases, and this increase is largely due to type 2 diabetes. In France in 2010, 40% of patients who started renal replacement...
therapy had diabetes, and of these 94% had type 2 diabetes. The total cost to the national health system was estimated to be €4 billion. Diabetic nephropathy is diagnosed as increased urinary albumin excretion (UAE) or decreased estimated glomerular filtration rate (GFR). In the US NHANES (National Health And Nutrition Examination Survey) study, the prevalence of diabetic nephropathy (reduced GFR, increased UAE, or both) was 43%. In France, 29%-47% of people with type 2 diabetes have diabetic nephropathy. In the USA in the last two decades, there has been a significant reduction in all diabetic chronic complications—as a consequence of an improvement in diabetes management—with the exception of diabetic nephropathy. Thus, risk of diabetic nephropathy is not decreasing among patients with type 2 diabetes, despite guidelines recommending screening and nephroprotective care.

Microalbuminuria precedes overt proteinuria and was once considered the first clinical manifestation of diabetic nephropathy; however, the natural history of the disease may have changed. In the early 1980s, the risk of progression to overt proteinuria (albumin excretion rate (AER) >200 μg/min) over a decade in microalbuminuric type 1 diabetic patients was estimated to be about 80%. However, more recently, prospective studies have demonstrated that the percentage of type 1 diabetic patients with microalbuminuria progressing to overt proteinuria over 10 years is only around 30%. Due to initial overestimation of risk in earlier studies, improved prognosis due to advancements in treatment, or both. In fact, the concept that microalbuminuria spontaneously regresses to normoalbuminuria in a substantial proportion of patients is now well established. In type 2 diabetes, the progression rate from microalbuminuria to proteinuria is similar (around 30% over 10 years). In the Steno 2 study, over a 7.8 year follow-up of 151 type 2 diabetic patients with microalbuminuria, 31% progressed to proteinuria, 31% regressed to normoalbuminuria, and 38% remained microalbuminuric.

It is interesting that the rate of decline of GFR was much lower in patients who regressed to normoalbuminuria (2.3 mL/min/year) than in patients who progressed to proteinuria (5.4 mL/min/year), suggesting that regression to normoalbuminuria is associated with preservation of renal function. Renal outcome was associated with baseline AER levels, retinopathy status, metabolic and blood pressure control, and use of renin-angiotensin system (RAS) blockade.

Key modifiable risk factors for diabetic nephropathy include hyperglycemia, hypertension, dyslipidemia, anemia, albuminuria, and lifestyle factors, such as obesity and smoking. Early identification of key risk factors and prompt therapeutic intervention can potentially prevent or slow the decline of renal function in patients with type 2 diabetes mellitus. Large, long-term clinical trials have demonstrated that improved blood glucose control and blood pressure control (the latter especially with RAS blockers), the natural history of diabetic nephropathy has changed in the last few decades. Thus, it may now be possible to delay or halt the progression towards ESRD in patients with overt diabetic nephropathy. This contrasts with the concept that by the time patients have overt nephropathy, decline of renal function is unavoidable and inexorable. Glycemic control is the main risk factor for diabetic nephropathy, and strict glycemic control is the most potent therapeutic approach for preventing the development of nephropathy. When the clinical manifestations of diabetic nephropathy are present, blood pressure control is crucial, especially that obtained using RAS blockers. Nevertheless, the reduction in progression to ESRD achieved with RAS blockade in type 2 diabetes patients is not satisfactory. Recent data from the ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation) study support the importance of glycemic control in preventing the transition from microalbuminuria to proteinuria and from proteinuria to ESRD. The long-term follow-up of this trial demonstrated a sustained reduction over 10 years in the risk of dialysis and transplantation. It thus appears that intensive glycemic control is effective not only at preventing the development, but also at slowing the progression of diabetic nephropathy to ESRD. We have demonstrated that prolonged normoglycemia, obtained with pancreas transplantation alone, leads to the reversal and cure of established diabetic nephropathy lesions in patients with type 1 diabetes. Thus, glycemic control is crucial to the development, progression, and regression of diabetic nephropathy.

Pathophysiology
Although numerous factors contribute to diabetic nephropathy, it is well established that exposure to hyperglycemia is necessary for the development of this disorder. Studies in

### SELECTED ABBREVIATIONS AND ACRONYMS

<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ADVANCE</td>
<td>Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation</td>
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<tr>
<td>AER</td>
<td>albumin excretion rate</td>
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<tr>
<td>Epi N/glom</td>
<td>absolute number of podocytes per glomerulus</td>
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<td>ESRD</td>
<td>end-stage renal disease</td>
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<td>FPW</td>
<td>foot process width</td>
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<tr>
<td>FSLv/glom</td>
<td>length density of filtration slits over the peripheral glomerular basement membrane</td>
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<tr>
<td>GBM</td>
<td>glomerular basement membrane</td>
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<tr>
<td>GFR</td>
<td>glomerular filtration rate</td>
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<tr>
<td>NHANES</td>
<td>National Health And Nutrition Examination Survey</td>
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<tr>
<td>Nv(epi/glom)</td>
<td>density of podocytes per glomerulus</td>
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<td>RAS</td>
<td>renin-angiotensin system</td>
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<td>UAE</td>
<td>urinary albumin excretion</td>
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<td>Vv(mes/glom)</td>
<td>mesangial fractional volume</td>
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type 1 and type 2 diabetes have found that improved glycemic control can reduce the risk of diabetic nephropathy. Moreover, the development of the earliest diabetic renal lesions can be slowed or prevented by strict glycemic control, as was demonstrated in a randomized trial in type 1 diabetic kidney transplant recipients. In addition, intensive insulin treatment has been shown to decrease the progression rates of glomerular lesions in microalbuminuric type 1 diabetic patients. Regression of established diabetic glomerular lesions was demonstrated in the native kidneys of type 1 diabetic patients with prolonged normalization of glycemic levels after successful pancreas transplantation. These studies strongly suggest that hyperglycemia is necessary not only for diabetic nephropathy lesions to develop, but also for the maintenance of established lesions. Removal of hyperglycemia allows expression of reparative mechanisms, which ultimately result in the healing of the original diabetic glomerular injury.

Hemodynamic mechanisms may be also involved in the pathogenesis of diabetic nephropathy. Interestingly, patients with other causes of hyperfiltration, such as uninephrectomy, do not develop diabetic lesions. Therefore, glomerular hyperfiltration alone cannot explain the genesis of the early lesions of diabetic nephropathy. Clinical observations suggest that hemodynamic factors may be more important in modulating the rate of progression of already well-established diabetic lesions. It is worth noting that the presence of reduced GFR in normoalbuminuric patients with type 1 diabetes has been associated with the presence of more severe glomerular lesions, and these patients may be at increased risk of progression to overt diabetic nephropathy. Systemic blood pressure levels are implicated in progression and may be implicated in the genesis of diabetic nephropathy. Intensive blood pressure control has been associated with decreased rates of progression from normoalbuminuria to microalbuminuria and from microalbuminuria to proteinuria in both normotensive and hypertensive type 2 diabetic patients.

Genetic predisposition to diabetic nephropathy has been strongly suggested by multiple cross-sectional studies in type 1 and type 2 diabetic siblings concordant for diabetes. Importantly, diabetic sibling pairs known to be concordant for diabetic nephropathy risk are highly concordant for diabetic glomerulopathy lesions. This risk, in part independent of glycemia, seems to be substantial. Searches for genetic loci related to susceptibility to diabetic nephropathy are ongoing with genomic scanning and candidate gene approaches, although neither approach has yet yielded definitive results.

Renal lesions of diabetic nephropathy appear to be mainly related to extracellular matrix accumulation, which occurs in the glomerular basement membrane (GBM) and in the tubular basement membrane and is the principal cause of mesangial expansion and a contributor to interstitial expansion late in the disease. Several regulatory mechanisms have been proposed to explain the linkage between high glucose levels and extracellular accumulation. These include: increased levels of transforming growth factor β; activation of protein kinase C; stimulation of extracellular matrix production through the cyclic adenosine monophosphate pathway; increased levels of advanced glycation end products; and increased activity of aldose reductase, leading to the accumulation of sorbitol. There is also growing evidence that oxidative stress increases in diabetes and is related to diabetic nephropathy. There is an association between oxidative stress, altered nitric oxide production and action, and endothelial dysfunction.

Pathology

The renal lesions underlying renal dysfunction differ between type 1 and type 2 diabetes, although the clinical manifestations of diabetic nephropathy—proteinuria, decreased GFR, and increased blood pressure—are similar. Indeed, in type 1 diabetes, although tubular, interstitial, and arteriolar lesions are present, the most important structural changes involve the glomerulus. In contrast, a substantial proportion of type 2 diabetic patients have normal glomerular structure with or without tubulointerstitial and arteriolar abnormalities, despite the presence of microalbuminuria or proteinuria. The clinical manifestations of diabetic nephropathy are strongly related to structural changes, especially the degree of mesangial expansion in both type 1 and type 2 diabetes. In the last few years, changes in the structure and number of podocytes have also been linked to the progression of diabetic nephropathy.

Type 1 diabetes

Renal morphologic lesions of diabetic nephropathy in type 1 diabetic patients occur in the glomeruli, arterioles, interstitium, and tubules. In type 1 diabetes, glomerulopathy is the most important lesion, characterized by thickening of the GBM and mesangial expansion, although the tubules, interstitium, and arterioles also undergo substantial changes (Figure 1, page XXI). GBM thickening, the first measurable change, has been documented as early as 1.5 to 2.5 years after the onset of type 1 diabetes. Mesangial expansion develops later; an increase in the matrix component of the mesangium can be detected as early as 5-7 years after the onset of diabetes. Thereafter, these structural changes do not develop at the same rate in individual patients. Nevertheless, when renal insufficiency occurs, marked mesangial expansion and increased GBM width are present in all type 1 diabetic patients. Diffuse and generalized mesangial expansion, commonly termed diffuse diabetic glomerulosclerosis, is associated with nodular lesions consisting of areas of marked mesangial expansion forming large, round fibrillar mesangial zones with palling of mesangial nuclei around the periphery of the nodule and extreme compression of the associated glomerular capillaries (Kim-
melstiel-Wilson nodules). Both mesangial expansion and GBM thickening are consequences of extracellular matrix accumulation, with increased deposition of collagen (types IV and VI), laminin, and fibronectin. Additional structural abnormalities include glomerular enlargement, tubular basement membrane thickening, tubular atrophy, interstitial expansion, and afferent and efferent arteriolar hyalinosis.2,32-34 Bowman’s capsule thickening is also regularly present.

Type 2 diabetes

In type 2 diabetes the situation is more complex. We studied a large cohort of type 2 diabetic patients with microalbuminuria and proteinuria and described heterogeneity in renal structure among these patients; in fact, only a subset had diabetic glomerulopathy, while the remaining had mild or absent glomerulopathy with or without tubulointerstitial and arteriolar changes.33,35 In proteinuric patients, less than 10% had nondiabetic renal diseases. thus, we proposed a classification system based on 3 major groups33,35:

- Category C I: normal or near normal renal structure
  These patients (representing 35% of cases of microalbuminuria and 15% of proteinuria) had biopsies that were normal or showed very mild glomerular, tubular, interstitial, and vascular changes.

- Category C II: typical diabetic nephropathology
  These patients (representing 30% of cases of microalbuminuria and 50% of proteinuria) had established diabetic lesions, with an approximately equal degree of glomerular, tubulointerstitial, and arteriolar changes. This picture is typical of that seen in type 1 diabetic patients with obvious diabetic nephropathy changes using light microscopy.

- Category C III: atypical patterns of renal injury
  These patients (representing 35% of cases of microalbuminuria and 35% of proteinuria) had relatively mild diabetic glomerular changes considering the disproportionately severe renal structural changes, including: (i) tubular atrophy, tubular basement membrane thickening and reduplication, and interstitial fibrosis (tubulointerstitial lesions); (ii) advanced glomerular arteriolar hyalinosis commonly associated with atherosclerosis of larger vessels; and (iii) global glomerular sclerosis. In the C III group, these patterns were present in all possible combinations (Figure 2).

It thus seems that hyperglycemia may cause different patterns of renal injury in type 2 diabetic patients compared with type 1 diabetic patients. Tubulointerstitial and vascular changes could also be related to aging, atherosclerosis, and systemic hypertension. However, hypertension was present in almost all patients in all three structural categories, and “per se” cannot account for the different lesions observed in catego-
ry C III. Furthermore, mean age was similar in the patients in category C II and C III (60 years), despite different patterns of renal injury in the two groups, and our observations in a large number of age-matched normal controls indicate that aging by itself is not sufficient to explain most of the renal structural changes observed in C III patients. Thus, heterogeneity in renal structure might reflect the heterogeneous nature of type 2 diabetes.

**Structural-functional relationships**

The relationships between structural abnormalities and kidney function are better defined using electron microscopy morphometric analysis. The critical lesion in type 1 diabetes is mesangial expansion, morphometrically termed mesangial fractional volume (Vv(mes/glom)); this is the structural parameter that best correlates with all functional parameters in type 1 diabetes. Indeed, a highly significant inverse correlation exists between Vv(mes/glom) and GFR; when mesangium expands it restricts and distorts glomerular capillaries and diminishes capillary filtration surface, which is strongly directly related to Vv(mes/glom) and inversely to GFR. Vv(mes/glom) is also related to AER and blood pressure levels. In contrast, GBM thickening is not related to GFR or to the presence of hypertension, but only to AER, suggesting that this lesion is involved in the pathogenesis of albuminuria rather than the loss of kidney function. Interstitial expansion and percentage of global sclerosis are also related to proteinuria, hypertension, and declining GFR. In the early stages of diabetic nephropathy, however, our data in a small number of patients with type 1 diabetes studied with sequential renal biopsies indicate that progression from normoalbuminuria to microalbuminuria and from microalbuminuria to early overt nephropathy is related only to progressive mesangial expansion; by contrast, there was no progression in interstitial fibrosis or GBM thickening.

Mesangial expansion and interstitial expansion are independent determinants of renal dysfunction in type 1 diabetes and are probably the consequence of different pathogenetic mechanisms. Indeed, mesangial expansion is mainly due to extracellular matrix accumulation; this differs from early interstitial expansion, which is due to an increase of the cellular component. Increased interstitial collagen occurs only in patients with advanced diabetic nephropathy. Thus, in type 1 diabetes, clinical nephropathy is always associated with advanced glomerular injury.

In type 2 diabetes, our findings indicate that mesangial expansion is also a crucial structural change leading to loss of renal function. Although these structural-functional relationships were significant, they were imprecise and less strong than in type 1 diabetes. Moreover, in confirmation of our observations from light microscopy studies, glomerular lesions were less advanced in type 2 than type 1 diabetic patients, and a substantial number of these type 2 patients had normal glomerular structure despite abnormal AER. These data are in agreement with those from a study of Pima Indians, where global glomerular sclerosis, Vv(interstitium), and GBM width were similar in patients with long-term type 2 diabetes with normoalbuminuria and those with microalbuminuria; only Vv(mes/glom) increased from early diabetes to microalbuminuria. In these patients, ultrastructural glomerular parameters were significantly abnormal only in patients with clinical nephropathy.

Hayashi et al reported renal structural-functional relationships in type 2 diabetic patients similar to those observed in type 1 diabetes. In contrast, Osterby et al described great variability in glomerular injury in Danish type 2 diabetic patients with proteinuria; they also observed that type 2 diabetic patients tended to have less marked glomerular changes than type 1 diabetic patients with comparable renal function.

Heterogeneity in renal structure is related to the risk of progressive GFR loss. Over 4 years of follow-up, decline in GFR in type 2 diabetic patients with microalbuminuria and proteinuria was significantly correlated with the severity of mesangial expansion and GBM thickening.

**Role of podocytes in diabetic nephropathy**

Podocytes are injured in numerous experimental and human glomerular diseases, including diabetes. White et al observed similar numbers of podocytes in normal subjects and in type 1 diabetic patients with abnormal AER, although there was a trend towards fewer podocytes per glomerulus in diabetic patients. Moreover, this study found no significant correlation between podocyte number and AER. These findings contrast with those of a previous study reporting that podocyte number decreased in type 1 diabetic patients with normal AER compared with normal controls, suggesting that diabetes per se may affect podocytes. Biorn et al described an increase in foot process width (FPW) in the peripheral GBM of type 1 diabetic patients with abnormal AER compared with normoalbuminuric patients, without significant differences between microalbuminuric and proteinuric patients. Low podocyte number has also been described in type 2 diabetic Pima Indians with proteinuria.

It has been suggested that in these patients podocyte loss and increased foot process width play a role in the progression to overt nephropathy. This concept was reinforced by findings from a longitudinal study, in which Pima Indians with type 2 diabetes and microalbuminuria were studied over 4 years; the number of podocytes per glomerulus at baseline was the strongest predictor of changes in albuminuria, in that patients with the lowest number of podocytes had the highest risk of fast progression to overt proteinuria. We studied podocyte structure in a large cohort of Caucasian type 2 diabetic patients, with AER ranging from normal to overt proteinuria. The density of podocytes per glomerulus, Nv(epi/glom),
was significantly lower in all diabetic patients compared with controls, and was lower in microalbuminuric and proteinuric patients than in normoalbuminuric ones. The absolute number of podocytes per glomerulus (Epi N/glom) was lower in microalbuminuric and proteinuric patients compared with controls; however, there were no significant differences between the diabetic groups. In addition, microalbuminuric and proteinuric patients had decreased length density of filtration slits over the peripheral GBM (FSLv/glom) and increased FPW compared with normoalbuminuric patients. AER was inversely related to Nv(epi/glom) and FSLv/glom and directly related to FPW, while there was no correlation with Epi N/glom. GFR was weakly related only to FSLv/glom. These results suggest that in Caucasian type 2 diabetic patients changes in podocyte structure and density occur from the early stages of diabetic nephropathy and might contribute to increasing albuminuria in these patients. Structural changes in podocytes could in part explain abnormal albuminuria in patients without diabietic glomerulopathy. These findings also suggest that in type 2 diabetic patients, the density of podocytes may be functionally more relevant than their absolute number.

Podocytes have limited capacity to replicate and when they are lost they cannot be replaced by new cells; thus, it has been hypothesized that the loss of podocytes, along with the increase in glomerular volume caused by diabetes, necessarily requires the residual cells to cover a larger area of GBM. This could cause foot process widening and reduce the ability of the podocytes to remain attached to GBM, forming areas of bare GBM with consequent proteinuria. These areas are potential starting points for glomerular sclerosis.

Further studies on podocyte ultrastructure and on the expression of slit diaphragm proteins are necessary to better define the role of these cells in the pathogenesis of diabetic nephropathy.
La néphropathie diabétique est la cause la plus courante d’insuffisance rénale terminale dans le monde. Le contrôle de la glycémie et de la pression artérielle diminue le risque de développer cette complication. Cependant, une fois la néphropathie diabétique installée, seul le ralentissement de sa progression est possible. Au cours de ces dernières décennies, toutes les complications chroniques diabétiques ont significativement diminué sauf la néphropathie diabétique. Donc, malgré les recommandations en faveur du dépistage et des traitements nérophroprotecteurs, le risque de néphropathie diabétique ne diminue pas parmi les diabétiques de type 2. Les lésions rénales responsables de la dysfonction rénale diffèrent selon le type de diabète, 1 ou 2, mais les manifestations cliniques de la néphropathie diabétique (protéinurie, taux de filtration glomérale diminué, pression artérielle augmentée) sont similaires. Dans le diabète de type 1, malgré la présence de lésions tubulaires, interstitielles et artériolaires, c’est le glomérule qui pré-sente les modifications structurales les plus importantes, contrairement au diabète de type 2 dans lequel, chez la plupart des patients, la structure glomérale est normale avec ou sans anomalies tubulo-interstitielles et artériolaires en dépit de la présence de micro-albuminurie ou de protéinurie. Les manifestations cliniques de la néphropathie diabétique sont fortement reliées aux modifications structurelles en particulier le degré de l’expansion mesangiale dans le diabète de type 1 et de type 2. La progression de la néphropathie diabétique peut aussi être liée aux changements de structure et de nombre de podocytes, surtout dans le diabète de type 2.

**Keywords:** diabetes; mesangial expansion; nephropathy; pathophysiology; podocyte; proteinuria
The prevalence of heart failure (HF) and diabetes mellitus (DM) is increasing exponentially worldwide. The coexistence of these diseases, which confers a worse prognosis than HF or DM alone, identifies a large population at very high cardiovascular risk. Intuitively, reducing glucose levels appears a way of improving clinical outcomes in HF patients with DM, as glucose lowering is a therapeutic target in diabetes treatment and many effective glucose-lowering agents are available for the control of hyperglycemia. However, recent studies have shown that some of these pharmacological agents are responsible for negative cardiovascular outcomes. Indeed, the use of “antidiabetic” drugs appears to be associated with an increased rate of HF events, which is higher than that of other undesirable cardiovascular outcomes, such as myocardial infarction. A cardiovascular outcomes dichotomy—characterized by an increase in the occurrence of HF outcomes, but a neutral effect or sometimes even decrease with regard to primary composite cardiovascular outcomes—has been observed.

Heart failure and diabetes: lessons from outcome studies

by C. Vitale and J. C. Kaski, Italy and United Kingdom

The prevalence of heart failure (HF) and diabetes mellitus (DM) is increasing exponentially worldwide. The coexistence of these diseases, which confers a worse prognosis than HF or DM alone, identifies a large population at very high cardiovascular risk. Intuitively, reducing glucose levels appears a way of improving clinical outcomes in HF patients with DM, as glucose lowering is a therapeutic target in diabetes treatment and many effective glucose-lowering agents are available for the control of hyperglycemia. However, recent studies have shown that some of these pharmacological agents are responsible for negative cardiovascular outcomes. Indeed, the use of “antidiabetic” drugs appears to be associated with an increased rate of HF events, which is higher than that of other undesirable cardiovascular outcomes, such as myocardial infarction. A cardiovascular outcomes dichotomy—characterized by an increased risk of HF, but a neutral effect on other cardiovascular outcomes—has been described with the use of “newer” glucose-lowering agents. The definition of “optimal” glucose control in patients with DM remains controversial, particularly in those with concomitant HF. Current evidence suggests that tight glycemic control, ie, glycated hemoglobin ≤7%, may be associated with worse survival rates and greater HF risk than less tight glucose control strategies, regardless of the agent used. Further research is required to clarify uncertainties regarding the best way to control glucose levels with glucose-lowering agents in patients with DM and HF.

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of DM is independently associated with the risk of developing HF, with a two-fold increase in risk in men and a five-fold increase in risk in women. Age, diabetes duration, insulin use, ischemic heart disease, and elevated serum creatinine have all been shown to be independent risk factors for the development of HF in patients with DM. A meta-analysis of 21 studies, involving 1,111,569 patients of whom 507,637 had DM, showed that during a follow-up ranging from 1 to 12 years, insulin use, glycemic control (ie, fasting glucose and glycated hemoglobin [HbA1c]), age, and coronary artery disease were variables associated with incident HF in patients with DM, suggesting the potential role of glycemic control and antidiabetic medications in the development of HF.

Altered glucose metabolism and established DM are known to contribute to structural and functional abnormalities of the heart, which may culminate in different degrees of cardiac dysfunction and ultimately lead to HF, not necessarily as a result of coronary artery disease, but also via other pathogenic mechanisms. Obesity, metabolic syndrome, dyslipidemia, hypertension, and renal impairment are all often associated with the occurrence of DM. Altered cardiac glucose metabolism can affect cardiac contractility, leading to left ventricular dysfunction, even in the absence of coronary artery disease or structural heart disease. Hyperglycemia and insulin resistance are known to contribute directly to cardiac dysfunction through mechanisms related to impaired microvascular endothelial function, abnormalities of cardiac metabolism (ie, shifting myocardial utilization of glucose toward fatty acid oxidation), increased myocardial fibrosis, deposition of advanced glycation end products, oxidative stress, proinflammatory state, lipid accumulation, and increased local activation of the renin-angiotensin-aldosterone system, as well as increased sympathetic nervous system activity (Figure 1).

The presence of DM in patients with HF is also widely recognized as an independent risk factor for hospitalization as well as poor clinical outcomes due to cardiovascular events.
and all-cause mortality. The suggestion that DM may be a predictor of poor clinical outcomes in patients with HF emerged from subgroup data analysis of the SOLVD (Studies Of Left Ventricular Dysfunction) trial, which showed that all-cause and cardiovascular mortality were higher in DM than in non-diabetic patients.

Both population studies and clinical trials have demonstrated that the presence of DM in HF patients markedly increases the risk of recurrent HF hospitalizations, hospital stay duration, and mortality compared with HF patients without DM.

In the CHARMC (Candesartan in Heart failure—Assessment of Reduction in Mortality and morbidity) study, DM emerged as the most deleterious prognostic factor and was associated with an approximate 2-fold increase in either death or the composite outcome of cardiovascular death and hospitalization for HF in insulin users, and a 50% increase in risk in non-insulin-dependent patients.

However, the interaction between DM and impaired clinical outcomes seems weaker in patients hospitalized for HF compared with outpatients, suggesting that the severity of HF and/or decompensation drive clinical outcomes to a larger degree than other risk factors. In population-based studies, such as the Framingham Heart Study, mortality in diabetic patients is 34% one year after the diagnosis of HF.

The excess mortality rate related to DM is applicable to both HF with or without preserved left ventricular ejection fraction (LVEF) and to ischemic or nonischemic HF.

Intuitively, managing hyperglycemia effectively appears to be a suitable way of improving clinical outcome in HF patients. Glucose lowering is one of the strategic targets of diabetes treatment. However, drastic reductions in plasma glucose may result in the development of HF even in the absence of structural heart disease. Indeed, the results of recent studies have raised uncertainty as to whether some glucose-lowering agents may actually be causing harm in HF patients with DM.

**Heart failure treatment in patients with diabetes**

Although no randomized clinical trials have been performed to date to specifically study the effects of pharmacological intervention in patients with HF and DM, current international guidelines for the treatment of HF and DM give special recommendations for the use of cardiovascular therapies in patients with coexistent HF and DM. These recommendations are based on subgroup analyses of existing randomized clinical trials, in which approximately 30% of patients usually have DM.

β-Blockers and angiotensin-converting enzyme (ACE) inhibitors (or angiotensin II receptor antagonists [ARBs] in patients intolerant to ACE inhibitors) have been shown to be beneficial in patients with DM, and their use is associated with reduced mortality and hospitalization in these individuals. ACE inhibitors and ARBs have either a neutral or beneficial effect on glycemia, but β1-selective β-blockers may negatively affect glycemic control, thus increasing the risk of future DM and also potentially blunting the physiologic adrenergic response to hypoglycemia. This may explain why despite the unquestionable, large body of evidence in favor of the use of β-blockers in HF patients with DM, these patients are currently less likely to be discharged from hospital on a β-blocker than non-diabetic patients with HF. Slow-release metoprolol succinate, bisoprolol, and carvedilol appear to be the most appropriate choices for management of patients with DM and HF.

Recent data suggest that treatment with low-dose mineralocorticoid receptor antagonist can reduce the risk of hospitalization and premature death in patients with persistent HF symptoms (ie, New York Heart Association [NYHA] class II-IV) and a LVEF ≤35%, even if they are receiving treatment with ACE inhibitors (or ARBs) and β-blockers. Careful surveillance of renal function is mandatory in these cases due to the increased risk of nephropathy with the use of these agents in patients with DM. Ixivabradine should also be added to conventional therapy in patients in sinus rhythm with a heart rate ≥70/75 bpm, with persistent HF symptoms (NYHA class II-IV).

The newer LCZ696 (angiotensin-neprilysin inhibitor) agent has recently been shown to reduce both cardiovascular death and hospitalization for HF in patients with HF, LCZ696, min-

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**Selected Abbreviations and Acronyms**

- **ACE**: angiotensin-converting enzyme
- **ARB**: angiotensin II receptor antagonist
- **CHARM**: Candesartan in Heart failure—Assessment of Reduction in Mortality and morbidity
- **DM**: diabetes mellitus
- **DPP-4**: dipeptidyl peptidase-4
- **GLP-1**: glucagon-like peptide 1
- **HbA1c**: glycated hemoglobin
- **HF**: heart failure
- **LVEF**: left ventricular ejection fraction
- **NYHA**: New York Heart Association
- **PROACTIVE**: PROspective pioglitAzone Clinical trial In macroVascular Events
- **RECORD**: Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes
- **SAVOR-TIMI**: Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus–Thrombolysis In Myocardial Infarction
- **SOLVD**: Studies Of Left Ventricular Dysfunction
- **VIVIDD**: Vildagliptin In Ventricular Dysfunction Diabetes
eralocorticoid receptor antagonists, and ivabradine have been all shown to be similarly effective in patients with or without DM and should be used whenever possible in HF patients in the presence or absence of DM. Current recommendations are that pharmacotherapy for HF should be similar in patients with or without DM.15,16

Glucose-lowering treatment in patients with diabetes and heart failure
Assessment of cardiovascular safety was not compulsory before 2008. However, following the controversy about the potentially harmful cardiovascular effects of thiazolidinediones, regulatory agencies such as the European Medicines Agency and the US Food and Drug Administration imposed the assessment of cardiovascular safety for all antidiabetic drugs.18,19 Importantly, the efficacy of these agents has usually been assessed from a glucose-lowering perspective, ie, glycemic control expressed as HbA1c. The cardiovascular safety of antidiabetic drugs was based on the assumption that treatments that effectively lower HbA1c have better cardiovascular outcomes. However, the inadequacy of this assumption has now become evident after large sample-size and longer follow-up studies failed to show a reduction in cardiovascular mortality and/or morbidity (including HF) in patients with DM receiving intensive glucose-lowering therapy. Indeed, a meta-analysis restricted to high quality studies (Jadad score >3) of 13 studies in 34 533 patients showed that intensive glucose-lowering therapy was not associated with a significant reduction in cardiovascular risk.20 In fact, quite the opposite was true: in HF risk (7.1% < HbA1c < 7.8%).22

In studies assessing the effect of more intensive glucose-lowering therapy, the presence of HF was often considered to be an exclusion criterion and the first study performed in patients with both DM and advanced HF (mean LVEF = 25%±7%) reported an inverse relationship between HbA1c and HF mortality, as the 2-year all-cause mortality rate for patients with HbA1c levels <7% was 35% compared with 20% for those with HbA1c >7% (P<0.01).21 These data have been further confirmed by a retrospective study in a large national cohort of 5815 veterans with DM and established HF, where a U-shaped association between HbA1c and mortality was observed, with increased risk of death at both higher and lower HbA1c levels in comparison with modest glucose control (7.1% < HbA1c < 7.8%).22

These results have highlighted the problem of increased HF risk in patients with DM receiving glucose-lowering therapy, which now needs to be addressed systematically. At present, regulatory agencies just require a demonstration of cardiovascular safety with respect to the end points of death, myocardial infarction (MI), and stroke, while HF outcomes such as incident HF and recurrent hospitalization for HF are not required primary prespecified cardiovascular end points.

This is despite the fact that the assessment of HF outcomes related to the use of glucose-lowering therapy is of particular importance because HF is a common finding of major prognostic relevance in patients with DM. Emerging data, in particular regarding thiazolidinediones and incretin-based therapies, have shown that the rate of HF outcomes can exceed that of acute MI. A dichotomous trend—characterized by an increase in the occurrence of HF outcomes, but a neutral effect on or sometimes even decrease in primary composite cardiovascular outcomes—has been observed.

Thiazolidinediones were the first class of new glucose-lowering therapy associated with an increased occurrence of cardiovascular events, which led to a radical change in the approval process for antidiabetic drugs by the regulatory agencies. The use of thiazolidinediones in large randomized clinical trials23,24 and in several meta-analyses (Table I, page 60) has been associated with a significant increase in the risk of HF.25-28

In both the PROACTIVE (PROspective pioglitAzone Clinical Trial In macroVascular Events)23 and the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes)24 trials, age, increased body mass index, renal dysfunction, and high systolic blood pressure were identified as independent predictors of HF. This suggests that elderly patients with obesity, increased body mass index, renal dysfunction, or hypertension should be closely monitored for signs and symptoms suggestive of HF when treated with thiazolidinediones. When all available data is considered, rosiglitazone is associated with a 20% greater risk in the occurrence of HF compared with pioglitazone. In a meta-analysis of 56 trials including 35 531 patients, rosiglitazone use was associated with an increased risk of MI (odds ratio [OR], 1.28; 95% confidence interval [CI], 1.02-1.63; P=0.04), but not with increased cardiovascular mortality.29

In an American observational, retrospective study of 227 571 Medicare beneficiaries aged 65 years or older, use of rosiglitazone was associated with an increased risk of stroke, HF, and all-cause mortality and increased the risk of the composite outcome of acute MI, stroke, HF, or all-cause mortality over a follow-up of 3 years.30

It is known that thiazolidinediones affect the distal nephron, causing sodium and water retention, but the exact mechanism underlying the development of HF is not well known.

Rosiglitazone has been withdrawn from the market in Europe, and its use has been restricted in the US, while pioglitazone is still available in both Europe and the US. On the basis of available data, current European guidelines on HF and DM as well as the US Food and Drug Administration recommend avoiding the use of thiazolidinediones in patients with coexisting DM and HF, at least in those with HF of NYHA class III or IV.15,16
Incretin-based therapies include treatment with glucagon-like peptide 1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors. While no adequate data on cardiovascular and HF outcomes related to the use of GLP-1 receptor agonists are currently available in patients with DM and HF, data from large randomized clinical trials and meta-analyses do exist for the DPP-4 inhibitors (Table I).

**Table I.** Randomized clinical trials and meta-analyses with thiazolidinediones vs placebo/active drugs reporting heart failure outcomes.

<table>
<thead>
<tr>
<th>Randomized clinical trial, year, and drugs</th>
<th>Patients</th>
<th>Primary CV end point</th>
<th>Risk of HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROACTIVE³³ (2005) Pioglitazone vs placebo + baseline GLT</td>
<td>5238 high-risk patients with preexisting MVD</td>
<td>CV composite† • HR 0.90 (95% CI, 0.80-1.02)</td>
<td>Any HF report • 11% vs 8% (P&lt;0.0001) HF with hospital admission • 6% vs 4% (P=0.007) HF without hospital admission • 5% vs 3% (P=0.003) Fatal HF • 1% vs 1% (P=0.63)</td>
</tr>
<tr>
<td>RECORD³⁴ (2009) Rosiglitazone vs active control (metformin + sulfonylurea)</td>
<td>4447 patients with DM</td>
<td>CV composite§ • HR 0.99 (95% CI, 0.85-1.16)</td>
<td>HF causing hospital admission or death • HR 2.10 (95% CI, 1.35-3.27)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Meta-analysis, year, and drugs</th>
<th>Patients</th>
<th>CV risk</th>
<th>Risk of HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lago et al³⁵ (2007) 7 TZD RCTs • 5 rosiglitazone (3 vs placebo) • 2 pioglitazone (1 vs placebo)</td>
<td>20 191</td>
<td>CV death (rosiglitazone) • RR 0.91 (95% CI, 0.63-1.32)</td>
<td>TZDs • RR 1.72 (95% CI, 1.21-2.42) Rosiglitazone • RR 2.18 (95% CI, 1.44-3.32) Pioglitazone • RR 1.32 (95% CI, 1.04-1.68) Fatal HF • 1% vs 1% (P=0.63)</td>
</tr>
<tr>
<td>Singh et al³⁶ (2007) 3 TZD RCTs 4 TZD ObStuds</td>
<td>10 731 (RCTs) and 67 382 (ObStuds)</td>
<td>CV death (rosiglitazone) • RR 0.91 (95% CI, 0.63-1.32) Rosiglitazone • RR 2.18 (95% CI, 1.44-3.32) Pioglitazone • RR 1.32 (95% CI, 1.04-1.68) Fatal HF • 1% vs 1% (P=0.63)</td>
<td></td>
</tr>
<tr>
<td>Hernandez et al³⁷ (2011) 10 TZD RCTs • 8 rosiglitazone • 2 pioglitazone</td>
<td>7331 (rosiglitazone) and 5804 (pioglitazone)</td>
<td>CV death (rosiglitazone) • RR 0.91 (95% CI, 0.63-1.32) Rosiglitazone • RR 2.18 (95% CI, 1.44-3.32) Pioglitazone • RR 1.32 (95% CI, 1.04-1.68) Fatal HF • 1% vs 1% (P=0.63)</td>
<td></td>
</tr>
<tr>
<td>Loke et al³⁸ (2011) CV outcomes comparing rosiglitazone vs pioglitazone in DM</td>
<td>429 000 (rosiglitazone) and 61 000 (pio- glitazone)</td>
<td>MI • OR 1.16 (95% CI, 1.07-1.24) Overall mortality • OR 1.14 (95% CI, 1.09-1.20)</td>
<td>HF • OR 1.22 (95% CI, 1.14-1.31)</td>
</tr>
</tbody>
</table>

All-cause mortality, nonfatal MI (including silent MI), stroke, ACS, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle. §CV hospitalization or CV death.

DPP-4 inhibitors have a neutral effect on cardiovascular outcomes, but increase the risk of incident HF and/or the risk of hospitalization for HF. Interestingly, a history of HF at baseline did not predict higher rates of cardiovascular disease outcomes or increased HF admission with DPP-4 inhibitors compared with placebo in either of the trials, although patients with a history of HF or higher pro–N-terminal brain natriuretic
### Table II. Randomized clinical trials and meta-analyses with dipeptidyl peptidase-4 inhibitors vs placebo/active drugs reporting heart failure outcomes.

<table>
<thead>
<tr>
<th>Randomized clinical trial</th>
<th>Patients</th>
<th>Primary CV end point</th>
<th>Risk of HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR TIMI 53 (2013)</td>
<td>16,492 patients with DM and history/risk of CV events</td>
<td>CV composite:  • HR 1.00 (95% CI, 0.89-1.12)  – P=0.99 for superiority  – P&lt;0.001 for noninferiority</td>
<td>HF hospitalization:  • HR 1.27 (95% CI, 1.07-1.51)</td>
</tr>
<tr>
<td>EXAMINE (2013)</td>
<td>5380 patients with DM and recent ACS</td>
<td>CV composite:  • HR 0.96 (upper boundary of one sided repeated CI, 1.16)  – P=0.32 for superiority  – P&lt;0.001 for noninferiority</td>
<td></td>
</tr>
<tr>
<td>EXAMINE (2015)</td>
<td>5380 patients with DM and recent ACS</td>
<td>CV death + hospitalized HF:  • HR 1.00 (95% CI, 0.82-1.21)  – CV death:  • HR 0.85 (95% CI, 0.66-1.10)  – Hospitalized HF:  • HR 1.19 (95% CI, 0.90-1.58)</td>
<td></td>
</tr>
<tr>
<td>VIVIDD (Unpublished)</td>
<td>254 patients with DM and symptomatic systolic HF with an LVEF &lt;35%</td>
<td>• No difference in adjudicated HF events</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>Patients</th>
<th>CV risk</th>
<th>Risk of HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monami et al (2014)</td>
<td>69,615</td>
<td>HF</td>
<td>OR 1.19 (95% CI, 1.03-1.37)</td>
</tr>
<tr>
<td>Clifton et al (2014)</td>
<td>100,200</td>
<td>HF outcomes (clinically significant HF/HF hospitalizations):  • RR 1.16 (95% CI, 1.01-1.33)</td>
<td></td>
</tr>
<tr>
<td>Wu et al (2014)</td>
<td>55,141</td>
<td>All-cause mortality:  • RR 1.01 (95% CI, 0.91-1.13)  – CV mortality:  • RR 0.97 (95% CI, 0.85-1.11)  – ACS:  • RR 0.97 (95% CI, 0.87-1.08)  – Stroke:  • RR 0.98 (95% CI, 0.81-1.18)</td>
<td></td>
</tr>
<tr>
<td>Savarese et al (2015)</td>
<td>85,224</td>
<td>MI:  • RR (&lt;29 weeks) 0.58 (95% CI, 0.36-0.94)  – RR (&gt;29 weeks) 0.94 (95% CI, 0.84-1.06)  – All-cause mortality:  • RR (&lt;29 weeks) 1.06 (95% CI, 0.56-2.01)  – RR (&gt;29 weeks) 1.01 (95% CI, 0.91-1.13)  – CV mortality:  • RR (&lt;29 weeks) 1.03 (95% CI, 0.51-2.07)  – RR (&gt;29 weeks) 0.96 (95% CI, 0.84-1.10)  – Stroke:  • RR (&lt;29 weeks) 0.67 (95% CI, 0.37-1.21)  – RR (&gt;29 weeks) 0.95 (95% CI, 0.79-1.14)</td>
<td>HF:  • RR (&lt;29 weeks) 0.67 (95% CI, 0.32-1.40)  – RR (&gt;29 weeks) 1.16 (95% CI, 1.01-1.33)</td>
</tr>
</tbody>
</table>

#CV death, MI, or ischemic stroke. §CV death, nonfatal MI or nonfatal stroke.

Abbreviations: ACS, acute coronary syndrome; CI, confidence interval; CV, cardiovascular; DM, diabetes mellitus; DPP-4I, dipeptidyl peptidase-4 inhibitor; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; RCT, randomized clinical trial; RR, relative risk.
International clinical guidelines recommend the use of metformin as first-line therapy in patients with both DM and HF. There is, however, a clear warning regarding its use in patients with severe renal failure, acute decompensated HF, or hepatic impairment. The well-known beneficial metabolic and cardiovascular effects of metformin (Table III) are consistently and unequivocally related to lower mortality rates with metformin compared with other glucose-lowering treatments (1-2 year mortality, 22% vs 34%; >4-year mortality, 38% vs 59%), lower rates of hospitalizations (all-cause hospitalization, 35% vs 64%; HF hospital admission, 34% vs 51%), and fewer adverse events.

Whether the use of insulin and sulfonylureas in patients with HF and DM is associated with an increased risk of HF is still controversial. A retrospective analysis of the Saskatchewan Health Database showed, in 1883 patients with DM and incident HF, that the use of sulfonylureas was associated with increased mortality (52% vs 33%) and hospitalizations (85% vs 77%) compared with the use of metformin. Furthermore, in 5631 patients with DM newly treated with a single oral agent and followed for 4.7±2.2 years, treatment with high-dose sulfonylurea was associated with a higher incidence of HF compared with treatment with high-dose metformin and lower daily doses (ie, lower than the median daily dose) of sulfonylurea. These results were confirmed in a study conducted in Denmark, in 10 920 patients hospitalized for HF for the first time and on treatment with metformin, sulfonylureas, and/or insulin, which showed that sulfonylureas or insulin were associated with a higher risk of mortality than metformin.

**Cardiovascular and metabolic effects of metformin**

- Insulin resistance, ↓ hyperinsulinemia
- Triglycerides, ↑ HDL cholesterol, ↓ LDL particle size
- Free fatty acids
- Blood pressure
- Vascular reactivity and endothelial function
- Improved ventricular remodelling
- Improved cardiac metabolism (↑ glucose oxidation, ↓ fatty acid oxidation)
- Plasminogen activator inhibitor-1 and platelet aggregation
- Vascular smooth muscle cell proliferation
- Neointimal proliferation after vascular injury
- Expression of adhesion molecules, metalloproteinases
- C-reactive protein, other inflammatory mediators
- Oxidative stress
- Carotid atherosclerosis (by IMT), ↓ aortic pulse wave velocity
- Atherosclerosis in animal models

**Table III. Cardiovascular and metabolic effects of metformin.**

Abbreviations: HDL, high-density lipoprotein; IMT, intima-media thickness; LDL, low-density lipoprotein.


peptide levels at baseline in the SAVOR-TIMI (Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus–Thrombolysis In Myocardial Infarction) study had a higher overall rate of HF admissions.

In addition, the VIVIDD (Vildagliptin In VentrIcular Dysfunction Diabetes) trial, which specifically recruited patients with DM and NYHA class I-III HF receiving HF guideline–recommend ed therapy, showed no difference between vildagliptin and placebo in the primary end point (LVEF assessed at 12 months) and, interestingly, no excess of HF hospitalizations.

Several mechanisms have been postulated to explain the negative impact of DPP-4 inhibitors on HF outcomes, including the occurrence of hypoglycemia, stimulation of the sympathetic and renin-angiotensin-aldosterone systems, and excessive glucose lowering (which seems to be the most important explanation).

To date, the only drug with beneficial effects on cardiovascular outcomes in patients with both DM and HF is metformin, which—in the past—was paradoxically contraindicated in patients with HF due to the potential risk of lactic acidosis. Clinical experience, post market surveillance, and observational work have shown that the risk is very low and similar to that of other antidiabetic drugs. Pooled data from 347 comparative trials and cohort studies have shown no cases of fatal or nonfatal lactic acidosis in 70 490 patient using metformin. More recently, a meta-analysis by Sheen et al confirmed the clinical safety and effectiveness of metformin even in patients with HF.
Juhaeri et al showed in 65,619 insulin-treated patients with DM that over a follow-up of 6 years the rate of HF is higher than that of stroke or MI (approximately double and triple, respectively). However, the risk of hypoglycemia and weight gain associated with sulfonylureas, as well as the risk of weight gain, sodium retention, and elevated blood pressure associated with insulin, have to be considered and monitored carefully in patients with coexistent DM and HF. In a recent meta-analysis of 14 trials enrolling 95,502 patients, all glucose-lowering therapies or modulation strategies increased the risk of HF compared with placebo or standard care (relative risk [RR], 1.14; 95% CI, 1.01-1.30; \( P=0.041 \)), with the highest risk observed in those using thiazolidinediones, followed by those treated with DPP-4 inhibitors, and with neutral effects in patients receiving insulin. “Old” anti-diabetic drugs seem safer than the “newer” agents in patients with concomitant DM and HF. Indeed, the latest agents have been shown, in randomized clinical trials, to increase the risk of HF, but to have a neutral effect on other cardiovascular outcomes. The reason for these results is not known and several confounding variables may have had an impact on these findings (Box 1).

**Conclusion**

In patients with coexisting DM and HF or with an increased risk of HF, a therapeutic strategy based on moderate glycemic control should be implemented, with the glucose-lowering agent metformin having a preferential role. The use of newer glucose-lowering therapies such as thiazolidinediones and incretin-based therapies should be avoided or used with strict cardiovascular monitoring in patients with HF or at increased risk of HF. The choice of anti-diabetic treatment in patients with DM and concomitant HF remains controversial, as the optimal level of glycemic control has yet to be established in these patients and more research is needed to determine this.

**References**

CHANGING THE NATURAL HISTORY OF TYPE 2 DIABETES:
IMPLICATIONS FOR CLINICAL CARE

La prévalence de l’insuffisance cardiaque (IC) et du diabète augmente de façon exponentielle dans le monde. La vaste population qui cumule ces deux maladies est à très haut risque cardio-vasculaire et son pronostic est moins bon que pour l’IC ou le diabète seuls. De façon intuitive, réduire la glycémie semble être une façon d’améliorer les résultats cliniques chez les patients IC, l’abaissement de la glycémie étant une cible thérapeutique dans le traitement de l’IC, mais un effet neutre sur d’autres effets cardio-vasculaires. La définition du contrôle « optimal » de la glycémie chez les diabétiques reste controversée, en particulier chez ceux qui ont une IC concomitante. D’après les données actuelles, un contrôle glyémique strict, c’est-à-dire une hémoglobine glyquée ≤ 7 %, peut s’associer à un moins bon taux de survie et à un plus grand risque d’IC qu’avec des stratégies de contrôle glyémique moins sévères, quel que soit le médicament utilisé. Il faudra d’autres études pour clarifier les incertitudes liées au vrai rôle du contrôle glyémique par hypoglycémiant chez des patients ayant un diabète et une IC.

Keywords: cardiovascular; diabetes mellitus; glycated hemoglobin; heart failure; outcomes
Do we focus enough on clinical outcomes when treating patients with type 2 diabetes?

Recent analyses have suggested that the management of type 2 diabetes is often fixated on addressing glucose-lowering and tolerability rather than micro- and macrovascular benefits, even though the ultimate goal for the subject with type 2 diabetes is to improve prognosis. While practicality is important for medicines used in diabetes, does evidence indicate that there should be more emphasis placed on these clinical outcomes when choosing a therapy?

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10. M. Rizzo, Italy
11. J. E. N. Salles, Brazil
In an attempt to explain why we are not particularly successful at treating type 2 diabetes mellitus (T2DM), despite the expenditure of enormous effort in achieving and maintaining optimal glycemic control, researchers have proposed the concept of “natural” history of the disease. In my opinion, there is nothing “natural” about the history of T2DM. The diabetes care system is simply too slow. Treatment initiation occurs too late, when a negative “legacy effect” is almost established. Even if glycemic control is achieved, there is little to no chance of changing anything.

Therefore, the time has come to seriously think about primary prevention in T2DM, maximizing early diagnosis and early initiation of the most effective, long-term, and safe ways to manage this severe and chronic disease.

Hyperglycemia is the hallmark of diabetes, and despite some discussion, glycemic control remains a major target for preventing chronic complications. The benefits of glycemic control have been clearly demonstrated in the United Kingdom Prospective Diabetes Study (UKPDS),1 which showed that intensive glucose-lowering treatment aimed at a target glycated hemoglobin (HbA1c) <7% was associated with a reduction in the risk of major vascular events, mainly microvascular, of 37%. A nonsignificant reduction in the relative risk of myocardial infarction of 16% was also observed. Similar results were obtained in the Kumamoto study.2

In ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation),3 the achievement of lower levels of HbA1c in the intensive treatment group compared with the standard treatment group (6.6% vs 7.3%) was associated with a clear reduction in the risk of combined major macro- and microvascular events (hazard ratio [HR], 0.9; 95% CI, 0.82-0.98; P=0.01). However, these results differ to those from other studies, like VADT (Veterans Affairs Diabetes Trial) and ACCORD (Action to Control Cardiovascular Risk in Diabetes).3,5 In the VADT study,6 mean HbA1c was reduced to 6.9% in the intensive group and 8.4% in the standard group. However, there was no significant between-group difference in the risk of cardiovascular events or glycemic control–related mortality (HR, 1.07; 95% CI, 0.81-1.42; P=0.62), as well as in the risk of microvascular events. ACCORD was terminated prematurely due to higher mortality associated with intensive glycemic control.5 Combined analysis of the three studies,6 nevertheless, showed that intensive glycemic control reduces the risk of cardiovascular disease without increasing the risk of mortality and that early intensive therapy delays the development and progression of diabetes complications.

Normal HbA1c values are often considered an indicator of adequate diabetic care, but this is a generalization that could be far from true in daily practice. HbA1c is a cumulative and integral indicator of glycemic status over the past 3 months; it does not reflect glucose fluctuations over 24 hours. 24-Hour variation in glucose level can be substantial and lead to severe complications.

Parameters of glycemic control do not reveal the actual duration of disease or status of pancreatic β cells, which is noteworthy as the efficacy of many treatments depends on the preservation of β cells.

The risk of macrovascular events rises in parallel with progression of diabetes, so it is crucial to take action early to reduce the risk of these events in the earliest stages of glycemic disturbance rather than when diabetes mellitus appears, by which time it is too late to regress the disease.

Long-term glycemic control over ≥11 years, as in the DCCT (Diabetes Control and Complications Trial), UKPDS, Steno-2, EDIC (Epidemiology of Diabetes Intervention and Complications), and ADVANCE-ON (Observational study)7–9 studies, is associated with a positive “legacy effect,” a reduction in the risk of microvascular events, and improvement in outcomes.

References
2. Ş. Çetinkalp, Turkey

Treatment initiation with metformin in patients with newly diagnosed type 2 diabetes is indispensable. All international guidelines have reached a consensus on this, and all combination therapies should contain metformin if there is no contraindication to its use. Is metformin indispensable because it is a more effective antihyperglycemic agent? Not really, according to the United Kingdom Prospective Diabetes Study (UKPDS) 34 report. Metformin couldn’t bring glycated hemoglobin (HbA1c) levels to glycemic target; it only reduced them by 0.6%. However, the use of metformin is justified by the considerable protection it affords from macrovascular complications of diabetes, reducing myocardial infarction by 39% and cerebral palsy by 41%. Moreover, it does this with a tolerable side effect profile and without causing weight gain or hypoglycemia. Despite these positive features and guideline recommendations, metformin was chosen as the first-line drug for only 56% of American type 2 diabetics, according to Berkowitz et al.1 Why is this?

In 2009, an important change was made to the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) guidelines. Add-on therapies to metformin were classified into two groups: well-validated core therapies and less-well-validated therapies.2 These evidence-based guidelines focused on the prevention of complications. Data from UKPDS, ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation), and VADT (Veterans Affairs Diabetes Trial) influenced the change in direction.

UKPDS showed that a reduction of 1% in HbA1c was associated with a 37% reduction in development of microvascular complications. However, application of an intensive approach for reaching the HbA1c targets did more harm than good in ACCORD and VADT; in the former study, severe hypoglycemia increased cardiovascular deaths by 35% and total mortality by 22%. In contrast, ADVANCE demonstrated that when HbA1c targets are reached without causing severe hypoglycemia using a safe antidiabetic agent, mortality does not increase and nephropathy and cardiovascular deaths were reduced by 21% and 12%, respectively. The impact of this finding was reflected in the treatment algorithm of the International Diabetes Federation 2011 guidelines on type 2 diabetes: “based on the use of gliclazide in the ADVANCE study, the first add-on to metformin therapy should be a sulfonylurea.”3 4

The favorable effects of gliclazide on nephropathy in ADVANCE and ADVANCE-ON (Observational study) were similarly reflected in the ADA/EASD 2012-2015 treatment guidelines.4 Their aim was to avoid severe hypoglycemia while treating hyperglycemia (based on individual HbA1c targets) as well as to prefer therapies, such as metformin and gliclazide, that reduce development of complications regardless of glycemic control. However, the new treatment algorithm of the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) 2015 guidelines on type 2 diabetes breaks this trend.5 These hypoglycemia-and-weight-focused guidelines state that the first add-on to metformin therapy should be glucagon-like peptide 1 agonists, dipeptidyl peptidase 4 inhibitors, or sodium/glucose cotransporter 2 inhibitors. Unfortunately, no long-term evidence-based studies exist to demonstrate that these options reduce diabetes complications regardless of glycemic control. Furthermore, the concept of patient-tailored treatment is restricted by reasoning that each diabetic individual is obese and insulin-resistant.

In conclusion, current type 2 diabetes treatment algorithms focus on hypoglycemia and obesity, which may lead to a decrease in effective HbA1c reduction and the percentage of patients who reach HbA1c target. When choosing an antidiabetic agent based on a mechanistic approach, not only should antihyperglycemic efficacy be considered, but diabetes complications also. Otherwise, we may in future encounter patients who have regulated blood glucose levels with developed diabetic complications.

References
The most frequent cause of death among patients with type 2 diabetes mellitus (T2DM) is cardiovascular disease, and we all know that today the dramatic increase in the prevalence of T2DM in the world raises the prospect of an increase in cardiovascular morbidity and mortality in the coming decades. Cardiovascular disease, the major cause of morbidity and mortality for individuals with T2DM, is the largest contributor to the direct and indirect costs of diabetes. Common conditions coexisting with T2DM (eg, hypertension and dyslipidemia) are clearly risk factors for cardiovascular disease, and diabetes itself confers independent risk.\(^1\)\(^2\)

The Emerging Risk Factors Collaborators study, which included multiple clinical trial data, estimated that, compared with nondiabetics, a diagnosis of T2DM reduces survival in a middle-aged man and 50-year-old woman by 5.8 and 6.4 years, respectively, and that 50% of the difference is explained by cardiovascular mortality.\(^3\)

These pieces of evidence suggest that there should be more emphasis on these clinical outcomes when choosing therapy and managing the global risk arising from T2DM in the short and long term. Although it is commonly recognized that diabetes is “glycemic by diagnosis,” but “predominantly cardiovascular” in its complications, management of T2DM in practice sometimes focuses exclusively on glucose lowering. In the majority of available records and surveys in our field, only a minority of patients (<10%) have been found to have all risk factors under control.\(^1\)\(^3\)

Control of individual cardiovascular risk factors prevents or slows cardiovascular disease in people with diabetes.\(^4\)\(^5\) Large benefits are seen when multiple risk factors are addressed globally. The long-term results of the Steno-2 study\(^7\) confirm the importance of multifactorial intervention with a particular focus on established risk factors, and it is now generally accepted that lipid-lowering therapy and blood pressure control are essential for lessening macrovascular risk in T2DM.

Also, the metabolic complications of hyperglycemia and hypoglycemia are a rare cause of hospitalization today and, as such, affect the cost of disease less than they once did. Patients are far more likely to be admitted for cardiovascular complications that are more costly and that require longer stays in hospital, specialized monitoring, and multiple treatments.

In 2008, the Food and Drug Administration established guidance for industry to ensure that drugs in development for T2DM should have a beneficial, or at least neutral, effect in relation to cardiovascular outcomes.\(^7\) This guidance had consequences on the practice activity of clinicians, by making them reconsider management in terms of a comprehensive strategy rather than one objective, normoglycemia, which had been shown to be too simplistic in the light of available evidence.

Randomized controlled trials have demonstrated that metformin and sulfonylureas are safe and that they reduce microand macrovascular complications. In contrast, the impact of new diabetes drugs on cardiovascular outcomes remains unclear, as novel drugs should in theory outperform current treatment strategies by providing evidence for efficacy in lowering clinically relevant end points.

It seems clear that a “glucocentric” approach alone is not enough to improve cardiovascular outcomes. The real challenge is to transmit to patients what diabetes means in terms of cardiovascular risk. It is crucial to make patients properly understand the benefit of optimal cardiovascular risk control with different measures, such as making healthy dietary choices, reducing excess weight, and participating in regular physical activity. All this, of course, without them forgetting to control blood glucose, blood pressure, and lipids by taking prescribed medication with good adherence and motivation to achieve personalized goals agreed with their doctors.

References
In 2015, the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) published an updated position statement for the management of patients with type 2 diabetes mellitus. The update was necessary due to the growing number of new glucose-lowering medications and new data available from outcome trials and meta-analyses of big, randomized clinical trials in the previous three years. As Georgia does not have its own guidelines, doctors mostly use the ADA/EASD position statement. The new position statement, like the previous one, emphasizes personalization and individualization of treatment. Glycemic control remains a major focus of the treatment of patients with type 2 diabetes mellitus (T2DM). However, the pathogenesis of T2DM is complex, with multiple defects in numerous organs, and antihyperglycemic drugs are designed to target one or more of these pathophysiological defects. The number of noninsulin antihyperglycemic drugs is quite high; the most frequently prescribed ones are metformin, sulfonylureas, dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide 1 (GLP-1) agonists, pioglitazone, and most recently sodium/glucose cotransporter 2 (SGLT-2) inhibitors. Importantly, antihyperglycemic medication choice must be effective and well-tolerated, while avoiding hypoglycemia and weight increase.

Patients with diabetes are at increased risk of mortality and morbidity compared to the rest of the population. So, it is important that alongside good efficacy and tolerability, antidiabetic medication is safe. Based on the meta-analyses of rosiglitazone studies, the American Food and Drug Administration adopted guidance on evaluating cardiovascular risk in new antidiabetic therapy for T2DM in December 2008. Older drugs, such as metformin and sulfonylureas, have a long record of use in clinical practice. It is known from UKPDS (United Kingdom Prospective Diabetes Study) that metformin is likely to have a cardiovascular benefit. Sulfonylureas were once viewed with great concern with regard to increased risk of heart disease, but a recently performed meta-analysis of 28 trials with 34,912 patients proved that sulfonylureas do not increase the risk of all-cause mortality. Intensive glycemic control reduced the risk of nonfatal myocardial infarction, amputation of a lower extremity, and microvascular complications, but increased the risk of severe adverse events and severe hypoglycemia. There was no significant difference in health-related quality of life between the targeting of intensive versus conventional glycemic control. The ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation) trial has also demonstrated that an intensive strategy with conventional agents can achieve mean HbA1c levels of 6.5% safely, with no increase in mortality. It is true that there was no significant reduction in macrovascular disease, but the reduction in diabetic nephropathy of approximately 20% was evident. DPP-4 inhibitor trials show that these agents, with the exception of saxagliptin, do not increase the risk of hospitalization for heart failure; however, they showed no benefit regarding cardiovascular safety compared with placebo either. GLP-1 agonists and SGLT-2 inhibitors similarly have no cardiovascular safety benefit compared with placebo. Moreover, in rare cases, SGLT-2 inhibitors increase the risk of euglycemic ketoacidosis.

Every day we come to the conclusion that each patient differs and that every diabetes case is unique. Every time we are face to face with a patient in our office, we have to compare the risk and the benefit of each class of antidiabetic agent, taking into account all the data from randomized controlled trials and meta-analyses, and make a decision that best fits this individual patient.

References
Glucose control remains a major focus in the management of patients with T2DM, but its achievement should always be in the context of a comprehensive cardiovascular risk factor reduction program, which should include smoking cessation, the adoption of healthy lifestyle habits, blood pressure control, and lipid management. In general, guidelines on the management of T2DM recommend metformin as the first-line glycemia-lowering drug because of its possible beneficial impact on all-cause and cardiovascular mortality. In addition, this low-cost drug carries a low risk of hypoglycemia and is weight neutral. If glycated hemoglobin (HbA1c) target is not achieved after approximately 3 months, the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) recommend considering a combination of metformin and one of these six treatment options: sulfonylurea, thiazolidinedione, dipeptidyl peptidase 4 (DPP-4) inhibitor, sodium-glucose cotransporter 2 (SGLT-2) inhibitor, glucagon-like peptide 1 (GLP-1) receptor agonist, or basal insulin.2 In the latest World Health Organization model list of the most efficacious, safe, and cost-effective medicines—based on the needs of a basic health-care system—only two oral antidiabetic drugs are included: gliclazide and metformin.3

Ideally, glycemia-lowering drugs should be investigated and compared for their effects on hard end points, such as cardiovascular disease, death, and micro- and macrovascular complications. New studies suggest that commonly prescribed drugs for T2DM may not all be equally effective at preventing death and renal or cardiovascular diseases. Each drug has unique advantages and disadvantages, and the question is whether specific types of drugs should be preferred over others in terms of a better efficacy or safety profile.

Randomized controlled trials with DPP-4 inhibitors demonstrated no improvement in cardiovascular outcomes in patients receiving add-on therapy with saxagliptin, alogliptin, and recently sitagliptin versus placebo.4 The studies with saxagliptin and linagliptin showed that active treatment increased the risk of hospitalization for congestive heart failure.

The ADVANCE (Action in Diabetes and Vascular disease: PreterAX and Diabetes MR Controlled Evaluation) trial demonstrated in patients with T2DM that an intensive strategy with conventional agents (including gliclazide MR) can achieve mean HbA1c levels of 6.5% safely, with no increase in mortality. Despite no significant effect in reducing macrovascular disease, diabetic nephropathy was reduced by ~20%.5 The follow-up study, ADVANCE-ON (Observational study), demonstrated a persistent reduction in renal failure 5.5 years after return to usual care, without any increase or decrease in the risks of death or cardiovascular disease.6

If clinical practice guidelines are designed to facilitate informed decision-making, clinicians should perhaps focus more on the reduction of diabetic nephropathy and cardiovascular neutrality in patients with T2DM.

References

The publication of the United Kingdom Prospective Diabetes Study (UKPDS) in 1998 provided strong support to clinical practice that vigorous treatment of diabetes can decrease the morbidity and mortality of type 2 diabetes mellitus (T2DM) by decreasing its chronic complications. UKPDS also demonstrated that metformin reduced cardiovascular disease in a small subgroup that was overweight, and its postintervention follow-up demonstrated the long-term beneficial effects of intensive glucose control on macrovascular and microvascular events in patients with newly diagnosed type 2 diabetes at study entry.1

Other studies, however, in participants who had more advanced T2DM than those in UKPDS, such as ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular disease: PreterAX and Diamicron MR Controlled Evaluation), and VADT (Veterans Affairs Diabetes Trial), suggested no significant reduction in cardiovascular outcomes with intensive glycemic control.

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Experimental findings and preliminary clinical data suggest that DPP-4 (dipeptidyl peptidase 4) inhibitors, in addition to improved metabolic control, have the potential to interfere with the onset and progression of diabetic microangiopathy. However, these effects have not been confirmed in three large DPP-4 cardiovascular outcome studies—SAVOR (Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus), EXAMINE (EXAMINATION of cardiovascular outcomes with alogliptin versus standard of care in patients with type 2 diabetes mellitus and acute coronary syndromes), and TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin).

Health-care providers looking after diabetic patients should not only focus on the management of hyperglycemia, but should also address other cardiovascular risk factors to prevent cardiovascular disease. In addition to adequate glucose control, regular screening for retinopathy, measurement of microalbuminuria and estimated glomerular filtration rate, and foot examination can improve patient outcomes. Furthermore, the use of antidiabetic medications with microvascular benefit that has been proven in large randomized studies would be a valuable option.
Type 2 diabetes mellitus is one of the most important challenges facing contemporary medicine. There are about 400 million patients affected by this disease worldwide and its morbidity is constantly rising on all continents. The causes behind this growth in morbidity are complex: they involve population aging—a nonmodifiable phenomenon—but also factors like unhealthy diet, sedentary lifestyle, and obesity—all of which can potentially be modified or prevented. Type 2 diabetes is associated with premature mortality, mainly due to cardiovascular causes, as well as with disability, due to foot amputation, end-stage renal disease, or blindness.

The controversial question concerns whether in treating patients with type 2 diabetes, we are doing all that is possible to protect their health, prolong their life, and maintain their quality of life. Where should we look for answers to this question? The most important sources of information include large randomized controlled clinical trials whose aim was to examine the impact of various therapeutic interventions in patients with type 2 diabetes on clinically important end points, including mortality, cardiovascular events, microvascular complications, etc. It is key to emphasize that we are speaking about clinical studies that have evaluated outcomes that are important for patients and not just surrogates, for example, glycated hemoglobin level. Articles presenting the outcomes of such trials, with the exception of the United Kingdom Prospective Diabetes Study, have only been published recently, from 2008 onwards.³ What can we learn from their results?

Firstly, we have learned that while intensification of hypoglycemic therapy reduces the incidence of microvascular complications, like diabetic kidney disease (with its most advanced form, end-stage renal disease), there is no convincing evidence that proves that intensification reduces the risk of cardiovascular events or extends life expectancy, particularly in patients with longstanding type 2 diabetes with macroangiopathy. Secondly, when considering important clinical outcomes, it is difficult to prove the superiority of a specific glucose-lowering agent, including the newest generation ones, over other glucose-lowering agents.⁴ Although, there are very recent promising data that require further confirmation.⁴ Finally, it is important to treat typical comorbidities, in particular arterial hypertension, because this helps reduce cardiovascular morbidity.⁵ Although, in this case, therapeutic goals should be individualized and rational, as “the lower, the better” strategy has its limitations.⁶

Returning to the initial question—do we pay enough attention to the long-term clinical benefits of the therapeutic measures we apply in type 2 diabetes patients?

I believe this question is rhetorical—if the answer is to be given from the perspective of the entire system of diabetes care, it has to be negative. Many patients do not achieve glycemic goals and, moreover, for many they are incorrectly set (either too high or too low). It is not rare for comorbidities to be underdiagnosed and improperly treated. We must also keep in mind that the majority of type 2 diabetes patients are treated by primary care physicians, who might not be up to date with the newest information in diabetes treatment research, are often overworked, and are only able to devote a limited amount of time to diabetic patients. What can be done during this short visit to make these physicians look a couple or tens of years ahead?

There is no universal answer to this question. We need greater funds for diabetes care and changes in its organization, like giving greater responsibility and independence to educational nurses.⁷ We also need education at a number of levels—for society as a whole, health-care policy makers, all professionals caring for diabetes patients (diabetologists, primary care physicians, nurses, and dieticians)—and, last but not least, patients. After all, as Dr E. P. Joslin said many years ago, “The person with diabetes who knows the most, lives the longest.”

References
The ultimate aim of any approach in the management of diabetes is to enable patients to achieve better clinical outcomes and a better quality of life in the long term. For almost two decades, we have used the level of glycated hemoglobin (HbA1c) to reflect chronic glycemic control and assumed that reduction in HbA1c during treatment always translated into better clinical outcomes. This is not really true because we know from large clinical trials that clinical outcomes are influenced by: the history of previous glycemic control, baseline HbA1c, duration of diabetes, existing clinical complications, the methods by which lower HbA1c levels are obtained, and the side effects of the therapeutic agents; and not just by intensive glycemic control alone.1,2

There is evidence to demonstrate that the benefits of early and intensified control of diabetes on cardiovascular complications persist long after the cessation of intervention, despite the loss of within-trial differences in HbA1c levels. This implies that the effect of glycemic control on chronic vascular complications, in large part, depends on the previous history of glycemic control.3,4

Targeting intensive glycemic control in patients with diabetes and significant cardiovascular disease increases the risk of hypoglycemia and serious adverse clinical outcomes. Therefore, the choice of agents is very important if we must improve clinical outcomes in such patients.5 Nevertheless, in resource-constrained settings there is a need to balance the achievement of clinical outcomes while maintaining patient quality of life with the availability and affordability of antidiabetic agents. We have evidence from a large clinical trial and follow-on study, in which cheap antidiabetic drugs like metformin and a sulfonylurea demonstrated cardiovascular benefits.3,4

Standards in current type 2 diabetes guideline recommendations and the US Food and Drug Administration approval of new therapies for diabetes treatment base their conclusions on the premise that the level of HbA1c is equivalent to the rate of development of chronic diabetic vascular complications. However, they do not focus on the practicality of choosing drugs that reduce clinical outcomes.

The selection of any treatment for type 2 diabetes should focus on the achievement of better clinical outcomes and quality of life in the context of an individualized, patient-centered approach taking into consideration the stage of vascular disease at the time of glycemic control. It should incorporate evidence on treatment efficacy, proven benefits, and potential side effects. Furthermore, shared decision-making that includes the patient’s profile, needs, preferences, values, ability to pay, and beliefs are essential components of such an approach.

The major complication of type 2 diabetes is the development of cardiovascular disease, yet it is questionable whether our current glucose-lowering approaches focusing on surrogate markers of cardiovascular disease risk translate into a reduction in cardiovascular complications and cardiovascular mortality. The logical conclusion is that treatment and management of type 2 diabetes should be optimized towards reducing cardiovascular risk rather than simply focusing on reducing HbA1c and glucose levels to target values.

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The major aim of treating diabetes is to improve prognosis by decreasing micro- and macrovascular complications as well as other diabetes-related problems. Clinical trials of new medications have focused mostly on surrogate end points, such as blood sugar and glycated hemoglobin (HbA1c), and adverse effects related to them. However, to assess the clinical outcomes of any treatment strategy, time is necessary. This is illustrated by the decrease in cardiovascular disease in the newly diagnosed diabetic patients of the United Kingdom Prospective Diabetes Study, which only became evident after 30 years.1

Cardiovascular safety is the major concern of physicians in diabetes treatment because cardiovascular disease is the leading cause of morbidity and mortality in diabetes. The US Food and Drug Administration requires that the cardiovascular safety profile of every new diabetic medication must be assessed.

Most diabetic patients would die of cardiovascular diseases before reaching the end stage of renal disease (ESRD). ESRD and other microvascular complications have a huge impact on the quality of life of diabetic patients; retinopathy is the leading cause of blindness, while neuropathy is an important risk factor of foot ulcers. Approximately 40% of diabetic patients will have nephropathy, and half of this cohort will progress to ESRD in developed countries.2 Microvascular complications correlate strongly with blood sugar, and studies have shown that lowering blood sugar will significantly improve retinopathy, nephropathy, and neuropathy.3 The ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation) study,3 a randomized controlled, 2×2 factorial design trial comparing intensive glucose lowering to standard blood glucose control in chronic diabetic patients, showed that after a median follow-up of 5 years, proteinuria decreased significantly in the intensive treatment group, with an HbA1c of 6.5% vs 7.3% in the standard group.

The posttrial follow-up study, ADVANCE-ON (Observational study), found that progression to ESRD was 46% lower in the intensive group after another 5 years.4 However, there are still many other risk factors for micro- and macrovascular complications that must be considered, such as blood pressure, dyslipidemia, smoking, physical inactivity, and unhealthy diet. The Steno-2 study in type 2 diabetes with microalbuminuria reported a significant reduction in all cardiovascular risk factors. Nephropathy, retinopathy, and cardiovascular events decreased in the intensive treatment group when compared to the standard treatment group in the first 7.8 years of randomized controlled multifactorial intervention.5 These beneficial effects were sustained and continued to improve in the subsequent 5.5-year observational follow-up period in the intensive group, even though the two groups (intensive and standard control) had similar profiles with regards to HbA1c, blood pressure, and lipids. During the entire 13.3-year follow-up, the absolute reduction in death from any cause was 20%.6 Multiple targets must be reached in order to control diabetes effectively.

Diabetes is a very complex disease. Although randomized controlled trials are highly valued as a way of guiding the choice of medication to control blood sugar, these studies cannot cover all aspects of type 2 diabetes. Analysis of post hoc observational data provides the specialty with a broader view of daily practice. Consequently, clinical outcomes in cardiovascular disease as well as microvascular complications should be taken into account in order to obtain comprehensive care for diabetic patients.

References
T2D patients were randomly assigned to either standard glucose control or intensive glucose control (defined as the use of glulisine modified release, plus other drugs as required, to achieve a glycated hemoglobin value of 6.5% or less). After a median of 5 years of follow-up, the strategy of intensive glucose control with glulisine yielded a significant reduction in the combined outcome of major macrovascular and microvascular events.

It is clear that diabetes management does not only require glycemic control, but also the achievement of other therapeutic goals targeting all parameters that may reduce cardiovascular risk; monitoring such parameters in T2DM patients helps estimate the risk for the development of future complications. This also leads to treatment toward individualized clinical targets. Indeed, in clinical practice, physicians should consider the pharmacodynamic and pharmacokinetic properties of the drug and take into account all the patient’s other comorbidities, such as heart failure, renal disease, and liver disease, as well as his phenotype and social background. The advantages and disadvantages of a specific drug should be considered for each patient and, in this way, the eventual therapeutic approach chosen, including healthy lifestyle recommendations, will be individualized (patient-centered).

In the last few years, it has been suggested that cardiovascular medications, such as statins, may increase the development of new-onset diabetes; yet, data are still not conclusive.6 In summary, cardiovascular outcome remains a crucial point for T2DM patients that always needs to be considered in our daily clinical practice.

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The rate of insulinization was no greater with intensive versus standard treatment. No difference in the incidence of cardiovascular disease was observed between the groups, indicating that gliclazide MR does not increase medium- or long-term cardiovascular risk. The most important finding, however, was the large reduction in nephropathy in the intensive treatment group, in which end-stage renal disease (ESRD) was significantly reduced by 46% after ten years.

Diabetes is increasing exponentially as an important cause of hemodialysis in Brazil. Such a situation exists due to the lack of early, effective metabolic control of diabetes and because half those with diabetes do not know they have the disease. Early glycemic control in diabetes is a critical strategy for reducing ESRD. Nevertheless, blood glucose reduction should not be our sole focus; thought should also be given to the other beneficial effects of treatments. ADVANCE-ON shows that metabolic control can effectively be obtained with an oral antidiabetic agent (gliclazide MR), with additional benefits including low risk of hypoglycemia, good tolerability, and reduction in specific microvascular diseases, such as terminal kidney disease.

So, yes, we should focus more on clinical outcomes when treating patients with type 2 diabetes.

References

Intensive glycemic control has been extensively studied in recent years. The results of large trials, such as ACCORD, ADVANCE, and VADT, which compared strict versus conventional glycemic control, showed no difference in the incidence of cardiovascular disease or mortality (except in the intensive treatment arm of ACCORD, where mortality was higher). In contrast, the UKPDS study showed that intensive treatment was better at preventing heart attacks and reducing all-cause mortality. Similar data in type 1 diabetes were found in DCCT, a continuation of DCCT. With similar glycaemic hemoglobin levels in both groups, mortality was lower and cardiovascular disease progressed less with intensive treatment. The terms “metabolic memory” and “glycemic legacy” were used to describe the lower risk of complications and mortality with better early glycemic control. Chronic hyperglycemia may lead to the formation of mitochondrial reactive oxygen species (ROS) and the alteration of respiratory chain proteins. This alteration allows continuous ROS formation, even after correction of hyperglycemia, which promotes endothelial dysfunction and leads to diabetic complications, cardiovascular disease, and nephropathy. This being the case, early, intensive control of blood glucose is an important target in preventing mortality and complications in patients with diabetes.

Cardiovascular safety of oral antidiabetic agents
Clinical trials that assessed the cardiovascular safety of oral antidiabetic agents have also proven useful for assessing their possible side effects and benefits. For dipeptidyl peptidase 4 inhibitors, cardiovascular safety—but not reduction in diabetes-related complications—was demonstrated in SAVOR-TIMI, EXAMINE, and TECOS.

The cardiovascular safety of gliclazide modified release (MR) was shown in ADVANCE in patients with established type 2 diabetes and cardiovascular disease, a result that differentiates gliclazide MR from other sulfonylureas. In the 10-year follow-up trial, ADVANCE-ON, mean glycated hemoglobin was similar in both randomized groups (7.4%), allowing investigators to ascertain outcome benefits related to intensive treatment (including gliclazide MR) and not glycemic control.

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Treatment of type 2 diabetes needs to address disease progression and balance the pharmacological efforts that lower hyperglycemia against the increased risks of hypoglycemia and weight gain. Furthermore, as patients with type 2 diabetes are at increased risk of cardiovascular morbidity and mortality, treatment strategies should focus not only on reducing hyperglycemia, which decreases the risk of microvascular complications and probably also macrovascular complications, but also on controlling other cardiovascular risk factors and improving lifestyle factors. Findings show that greater benefits are obtained through an intensive target-driven approach to glucose control earlier in the life course of the patient. Modified-release gliclazide (gliclazide MR) has been shown to effectively lower HbA1c, with sustained glycemic control over time. In addition to its effective glucose-lowering action, gliclazide MR has been shown to significantly reduce the incidence of clinically relevant renal complications and is associated with the lowest risk of hypoglycemia and cardiovascular mortality among sulfonylureas. In view of its favorable risk-benefit balance and potential cardiovascular advantages, the Dutch Type 2 Diabetes Management Guidelines recently recommended gliclazide (rather than sulfonylureas as a class) as a preferred second treatment option.

Type 2 diabetes is one of the most prevalent and costly chronic medical conditions worldwide, incurring significant burdens on individuals, society, and health care systems. The global burden of diabetes has increased from 153 million people affected in 1980 to 387 million in 2014, and is expected to increase by a further 205 million over the next 20 years.¹

Type 2 diabetes is associated with long-term complications and reduced quality of life and life expectancy, and can result in a wide range of complications with repercussions for both the individuals and health care systems. People with type 2 diabetes have almost a twofold excess cardiovascular risk, including coronary artery disease (leading to heart attacks and/or angina); lower extremity peripheral artery disease (leading to amputations); and carotid artery disease (strokes, dementia).² In addition, prolonged hyperglycemia can lead to irreversible microvascular complications such as diabetic retinopathy, nephropathy, and neuropathy. The risk of death for adults with diabetes is 50% higher than for adults without diabetes and it is estimated that, globally, diabetes accounts for approximately 8.4% of deaths.


in adults aged 20-79 years, almost 5.1 million deaths annually. The presence of diabetic complications can lead to a 5-fold increase in a patient’s costs and people with diabetes can experience prolonged stays in hospital. Approximately 50% of people newly diagnosed with type 2 diabetes already have complications, so it is critical to implement some form of early intervention.

As patients with type 2 diabetes have an elevated risk of cardiovascular disorders, the treatment of this disease is multifactorial. Multiple vascular risk factors and wide-ranging complications make diabetes care complex and time-consuming, and many areas of health care services must be involved for optimal management. This means that treatment should focus not only on reducing hyperglycemia, which decreases the risk of microvascular complications and probably also macrovascular complications, but also on controlling other cardiovascular risk factors, such as smoking, hypertension, and dyslipidemia, and improving lifestyle factors, such as diet and exercise regimen to lose weight.

The risks of arterial disease and microvascular complications in people with diabetes are related to the extent of hyperglycemia over time. Because type 2 diabetes is a progressive condition, with secretion of insulin decreasing over time, the need for blood glucose-lowering therapy becomes imperative and inevitable. A comprehensive approach to blood glucose management incorporating education, assessment, self-monitoring, and pharmacological strategies is required to facilitate optimal care. Evidence points to an increased risk due to reduced life expectancy. The benefits, side effects, and relative cost-effectiveness differ among pharmacological classes, and to a lesser extent between individual drugs within the same class. The choice, order, and combination in which these treatments are used reflect consideration of their efficacy in glycemic control and prevention of microvascular and/or arterial damage, as well as their risks of side effects.

Mode of action of sulfonylureas

Type 2 diabetes results from two main pathological processes: insulin resistance and pancreatic β-cell dysfunction. Today, there are more therapy options for managing type 2 diabetes than ever before. As the first available oral glucose-lowering agents, sulfonylureas have a 60-year record of use, and there is substantial evidence of their efficacy, safety, and benefits in terms of quality-adjusted life-years at a significantly lower cost. The second-generation sulfonylureas such as glipizide, glibenclamide, gliclazide, and glimepiride, are still at the core of type 2 diabetes management with an early place in therapeutic algorithms. They are widely used around the world, accounting for up to 20% of newly initiated oral therapies, either as monotherapy or in combination, for treatment of type 2 diabetes.

The use of sulfonylureas to treat type 2 diabetes is based on their insulinotropic action on the pancreatic β cells. Their primary mechanism of action is to close ATP-sensitive potassium (KATP) channels in the plasma membrane of β cells, initiating a chain of events which results in insulin release. More recent studies have shown that the β-cell KATP channel is a complex of two proteins: a pore-forming subunit (Kir6.2) and a drug-binding subunit that functions as the receptor for sulfonylureas (sulfonylurea receptor 1 [SUR1]). It is the binding of the sulfonylurea to the common SUR receptor on β cells that causes the closure of the KATP channels and inhibition of potassium efflux, leading to membrane depolarization and influx of calcium. The SUR1 receptor contains two high-affinity binding sites, one that accepts a sulfonyl moiety and one that accepts a benzamide moiety. Studies of cloned channels have revealed that most sulfonylureas (glibenclamide, glipizide, and glimepiride) possess both sulfonyl and benzamide moieties (Figure 1) and interact with both binding sites, creating a tight and nonreversible bond to the SUR1 receptor. Gliclazide, however, has no benzamide moiety and only binds to the sulfonyl site and so dissociates from the receptor...
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Figure 1. Molecular structure of sulfonylureas.

more freely. These different binding behaviors result in different insulin secretion profiles, where the rapidly reversible interaction with gliclazide results in pulsatile stimulation. The consequence of prolonged binding, as with glimepiride, glipizide, and glibenclamide, is prolonged cell stimulation and uncontrolled insulin secretion.

This different binding behavior also has an impact on tissue selectivity and safety. K_ATP channels are found at high density in a variety of cell types other than the β cell, including cardiac, smooth, and skeletal muscle. Those sulfonylureas that contain both sulfonylurea and benzamide moieties (glipizide, glibenclamide, and glimepiride) bind and block both SUR1 and SUR2 K_ATP channels while, gliclazide blocks the SUR1 K_ATP channels in the β cell, but not SUR2A or SUR2B in cardiac or smooth muscle.

Gliclazide’s selectivity for the pancreatic β cell is important because the KATP channels in the heart are normally closed and open only in response to metabolic stress, such as that which occurs during ischemia. In the presence of cardiac ischemia, intracellular ATP levels drop, opening the cardiac muscle K_ATP channels and resulting in vasodilatation and decreased myocardial oxygen consumption, thereby minimizing tissue injury and protecting myocardial function. Nonselective pharmacological agents that close the cardiac SUR2A K_ATP channels oppose this ischemic preconditioning, effectively preventing this inherent protective effect and have the potential to increase cardiovascular risk in patients with diabetes.

More recent studies focused on glucagon-like peptide-1 (GLP-1) signaling have demonstrated a critical role for Epac2A (a cAMP binding protein) in the insulin secretory effect of incretins. The incretin GLP-1, secreted from the intestine upon meal ingestion, amplifies insulin secretion by binding to its specific receptors on pancreatic β cells, increasing the intracellular cAMP, and leading to the activation of both protein kinase A (PKA) and Epac2A/Rap1 signaling pathways. Epac2A has also been found to be a direct target of certain sulfonylureas and it was shown that activation of Epac2A/Rap1 signaling can potentiate sulfonylurea-induced insulin secretion.

The combination of an incretin and a sulfonylurea (glibenclamide or glimepiride) has been shown to synergistically stimulate insulin secretion at a basal level of glucose concentration through Epac2A/Rap1 signaling. Gliclazide is unique among sulfonylureas in that its effect is not influenced by Epac2A/Rap1 signaling, and these differences in the action of various sulfonylureas on Epac2A may well account for the clinical differences observed in the combinatorial effects of incretin and sulfonylureas. The incidence of hypoglycemia when a dipeptidyl peptidase-4 (DPP-4) inhibitor is combined with gliclazide is significantly lower than when it is combined with glibenclamide or glimepiride. These findings on the role of Epac2A/Rap1 signaling in the oversecretion of insulin observed with combination therapies suggest an additional mechanism for the differences observed in hypoglycemic risk depending on the sulfonylurea and its structure.

Glucose-lowering efficacy

Clinical experience with sulfonylureas

The degree of blood glucose lowering seen with sulfonylureas depends on the initial hyperglycemia, with a greater effect being seen in those with the highest initial glucose concentrations. Sulfonylureas have a long-standing evidence base for providing long-lasting improvement in blood glucose control. In placebo comparator studies, sulfonylurea treatment was found to reduce the fasting glycemia by 20 mg/dL to 40 mg/dL and HbA1c by 1.0 % to 2.0%, and a meta-analysis of 27 randomized clinical trials comparing different drugs added to...
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metformin found that sulfonylurea treatment was associated with a greater reduction of HbA1c than thiazolidinediones, and a similar effect to that of insulin.26 A recent systematic review and meta-analysis found sulfonylurea monotherapy to lower HbA1c by an average of 1.5%, similar to the reduction in HbA1c seen with metformin.27 Two more recent meta-analyses of randomized controlled studies have shown that gliclazide was slightly more effective in lowering HbA1c than other oral glucose-lowering agents, with a weighted mean difference between comparator of -0.11% to -0.13% (Figure 2).28,29

The UKPDS study (United Kingdom Prospective Diabetes Study) illustrated the progressive nature of type 2 diabetes with escalating rises in HbA1c over time as a result of progressive β-cell loss. While there were concerns that sulfonylureas might accelerate β-cell loss by stimulating an already strained islet, no differences in the rate of glycemic deterioration were observed between agents. As the glucose-lowering effect of sulfonylureas is secondary to increased insulin secretion, an adequate β-cell mass is needed. As more and more β cells are lost as part of the natural history of progression in type 2 diabetes, the efficacy of treatments are also reduced over the course of time.

In the ORIGIN trial (Outcome Reduction with an Initial Glargine Intervention), patients in the standard therapy group were treated mainly with metformin and a sulfonylurea, and glycemic control was maintained at an average HbA1c of 6.5% for 6 years.30 Overall, sulfonylureas do not appear to either increase or decrease the underlying rate of β-cell function decline, but results suggest that the “therapeutic failure” rate may not be similar in all sulfonylureas.

In the ADOPT study (A Diabetes Outcome Progression Trial), subjects treated with glibenclamide had the highest fasting glucose, HbA1c, insulin resistance, and failure rate of monotherapy. The therapeutic failure rate with gliclazide has been shown to be significantly lower than that of glibenclamide or glipizide.31 The ADVANCE trial (Action in Diabetes and Vascular disease: PreterAx and Dia-microN MR Controlled Evaluation) lowered the average HbA1c level to 6.5% in a broad range of patients with type 2 diabetes using an intensive gliclazide MR (Diamicron MR)–based glucose-control strategy, which was maintained (with 4 out of 5 patients attaining an HbA1c≤7%) with no deterioration for a mean of 5 years.32 Gliclazide’s durability of efficacy has also been documented in a study demonstrating that the delay before insulin depend-
ency (period until the start of insulin treatment) was significantly longer in patients with type 2 diabetes treated with gliclazide (14.5 years) than in those treated with glibenclamide (8 years).33

**Extrapancreatic effects**

Chronic oxidative stress is proposed to be a key component in the pathogenesis of diabetes as well as in the development of its complications.34 β Cells are extremely sensitive to oxidative stress and the excessive levels of reactive oxygen species (ROS) produced by chronic exposure to hyperglycemia is one of the main contributors to the deterioration of β-cell function over time.35,36 Gliclazide, with its free radical–scavenging aminoazabicyclo-octyl ring grafted on the sulfonylurea group, appears to be the only sulfonylurea that can reduce ROS production and apoptosis in β cells.37 Experiments in isolated islets exposed to various concentrations of sulfonylureas found an absence of β-cell apoptosis with exposure to gliclazide, whereas with glibenclamide and glimepiride the numbers of apoptotic cells were significantly increased.38 Moreover, only gliclazide prevented high glucose–induced apoptosis in human β cells.39

The free radical–scavenging properties of gliclazide may also help restore endothelial function and reduce platelet activity.40 Antiplatelet therapy has an established role in the management of people with cardiovascular disease, although its role in primary prevention for people without existing cardiovascular disease is less clear. By decreasing plasminogen activator inhibitor and enhancing fibrinolysis, gliclazide can inhibit platelet aggregation and thrombosis as well as lower blood viscosity, contributing to the prevention of microangiopathy.41

**Tolerability**

Tight glycemic control is essential in order to prevent or delay diabetes complications, but hypoglycemia is the foremost clinical concern when intensifying the treatment.3,42 Moderate hypoglycemia induces cognitive impairment42 and can interfere with many complex attention tasks relevant to everyday life, while recurrent severe hypoglycemia may induce more grave and long-term consequences.43,44 The glucose-lowering effect of sulfonylureas can lead to a severe hypoglycemic event in about 1 in every 100 persons per year.45 In the 10-year follow-up analysis of the UKPDS study, the annual incidence of at least one hypoglycemic event experienced by patients taking sulfonylureas was found to be less than half that occurring with insulin (17.7% vs 36.5%), while rates of major hypoglycemic episodes per year were 0.7% with conventional treatment, 1.4% with glibenclamide, and 1.8% with insulin.46

An intensive target-driven approach can, however, safely reduce the risk of complications in high-risk patients. As demonstrated in the ADVANCE trial, patients treated with gliclazide MR benefited from a significant reduction in combined macrovascular and microvascular complications (-10%, P=0.01), which was largely linked to a significant protection against new or worsening nephropathy (-21%, P=0.006).47 The rate of severe hypoglycemic events was only 0.7 event per 100 patients per year in the gliclazide MR active group and 0.4 event per 100 patients per year in the standard-control group. The low rate observed in the intensive group is particularly reassuring considering that 40% of patients were also on insulin therapy.

Individual sulfonylureas differ in their hypoglycemic potential, mainly due to their half-life and time of action and their affinity and binding behavior to the SUR1 receptor on β cells.48 A lower incidence of hypoglycemia has been reported with gliclazide than with other sulfonylureas in several studies. The GUIDE study (GLUcose control In type 2 diabetes: Diamicron modified release versus glimepiride), a 52-week double-blind comparison of gliclazide MR and glimepiride (the two most frequently used once-daily sulfonylureas in type 2 diabetes treatment), demonstrated that for similar reductions in HbA1c the proportion of patients experiencing hypoglycemic episodes was more than twice higher with glimepiride (8.9%) than with gliclazide MR (3.7%).49 Moreover, the particularly low incidence of hypoglycemia in the gliclazide MR–treated patients with only moderately elevated baseline HbA1c (≤7%), a group generally considered at higher risk for hypoglycemia, reinforces the value of gliclazide MR use to achieve the currently recommended aggressive HbA1c targets (between 6.5% and 7%).

Sulfonylureas differ in their binding behavior to the pancreatic β cell SUR1 receptor due to their different chemical structures and the presence—or absence—of a second active site (besides the sulfonyl moiety). Gliclazide has a rapidly reversible interaction with the receptor while glibenclamide, glimepiride, and glipizide exhibit prolonged binding and cell stimulation, which results in differences in tolerability.13,14

In terms of tolerability, the particular interest of gliclazide was highlighted in a recent meta-analysis of 22 randomized controlled studies comparing individual sulfonylureas. The analysis of mild hypoglycemic events (defined as blood glucose ≤3.1 mmol/L) showed that hypoglycemia was experienced by 10 times fewer patients in those taking gliclazide than in those taking glimepiride (1.4% vs 15.5%, P<0.001)48 (Figure 3, page 82). Likewise, a significantly lower proportion of patients experienced severe hypoglycemia when taking gliclazide (0.1%) than patients taking glipizide (2.1%), glimepiride (0.9%), or glibenclamide (0.5%).48 In addition, a network meta-analysis of randomized controlled trials found that when added to metformin, gliclazide confers the lowest risk of hypoglycemia among the sulfonylureas. Gliclazide reduced the comparative risk of hypoglycemia of any severity by 56% vs glimepiride, 85% vs glipizide, and 86% vs glibenclamide.49 Certain patients with type 2 diabetes, such as the elderly, those with renal impairment, or those on polypharmacy are
at increased risk of hypoglycemia.\textsuperscript{50} When caring for older adults with type 2 diabetes, particular consideration should be given to their broader health and social care needs. Older people are more likely to have coexisting conditions and to be on a greater number of medicines. The GUIDE study showed the same reduced risk with gliclazide versus glimepiride in older patients (>65 years) as that observed with younger patients. A more recent population-based retrospective cohort study evaluating the risk of hypoglycemia and all-cause mortality in older adults who were newly prescribed glibenclamide or gliclazide MR as monotherapy or in the presence of metformin found that gliclazide MR is associated with a significantly lower risk of hypoglycemia than glibenclamide.\textsuperscript{51} In matched comparison with glibenclamide, gliclazide was associated with a significantly reduced risk of severe hypoglycemia (8-fold reduction with monotherapy, and 6-fold reduction with bitherapy). Moreover, gliclazide MR treatment was associated with a significantly lower risk for hospital encounters with hypoglycemia than glibenclamide, all evidence supporting the current labeling where gliclazide MR is prescribed using the same dosing regimen recommended for patients under 65 years of age. These results in terms of efficacy and safety demonstrate that gliclazide is as effective as glibenclamide and glimepiride and more effective than glipizide in reducing HbA\textsubscript{1c} while causing less hypoglycemia than glibenclamide and glimepiride.\textsuperscript{52}

Kidney impairment also impacts the choice and dosage of medication and the referral strategy. Chronic renal failure is a progressive loss of function of nephrons that gradually decreases overall kidney function. The risk of hypoglycemia is increased in patients with substantial decreases in glomerular filtration rate (chronic kidney disease [CKD] stages 4 and 5) due to decreased clearance of insulin and of some of the oral agents used to treat diabetes. Progressive falls in kidney function result in decreased clearances of the sulfonylureas or their active metabolites, necessitating a decrease in drug dosing to avoid hypoglycemia. Unlike glibenclamide and glimepiride, gliclazide is metabolized by the liver (not the kidney) and does not have active metabolites, so it can be safely used in patients with mild-to-moderate renal insufficiency with the same dosing regimen as in patients with normal renal function.\textsuperscript{53} Moreover, the guidelines from the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative considers gliclazide a preferred sulfonylurea in patients with chronic kidney disease, with no dose adjustment necessary even in CKD stages 3, 4, and 5, including in dialysis and transplant patients.\textsuperscript{53}

Patients with type 2 diabetes that fast during Ramadan are also at increased risk of symptomatic and severe hypoglycemia, which can have an adverse effect on their quality of life, is a limiting factor in glycemic control, and forms an obstacle in compliance to medication and treatment. Current recommendations are largely based on expert opinion and not on scientific data derived from robust clinical trials. A recent meta-analysis of results from randomized trials comparing DPP-4 inhibitors and gliclazide (rather than the sulfonylurea class) highlighted similarly low risks of experiencing symptomatic hypoglycemia with either gliclazide or DPP-4 inhibitor, and pointed out that the proportion of patients reporting any hypoglycemic event in the gliclazide group was not statistically different than in the group of patients treated with sitagliptin or vildagliptin\textsuperscript{54} (Figures 4 and 5).

Two recent meta-analyses reexamined the evidence and came to similar conclusions: that the risk of severe or confirmed hypoglycemia is extremely low with gliclazide and that it has a much better safety profile than glibenclamide, glipizide, or glimepiride.\textsuperscript{28,29} An evaluation by an independent Dutch group validated their own country’s type 2 diabetes management guidelines, which specifically recommend gliclazide (“and not sulfonylureas as a group”) as the preferred second treatment option.\textsuperscript{55} Tissue selectivity and risk of hypoglycemia, which differ among sulfonylureas— with gliclazide consistently showing the lowest incidence—need to be considered when choosing a therapy.

Another major side effect that often limits the use of sulfonylureas is weight gain. In the UKPDS study, weight gain was significantly higher in the intensive group than in the conventional group, with patients assigned insulin gaining the greatest weight (4.0 kg) compared with those assigned glibenclamide (1.7 kg). Body weight was stable during the GUIDE study with mean changes from 83.1 to 83.6 kg and 83.7 to 84.3 kg on gliclazide MR and glimepiride, respectively, while the ADVANCE study showed that 5 years of intensive treatment with gliclazide MR resulted in no increase in body weight.\textsuperscript{32,47}
A retrospective analysis of 21,325 patients with type 2 diabetes followed over 5.5 years found that gliclazide was associated with a significantly reduced risk of acute coronary syndrome-related hospitalization compared with glibenclamide.

Evidence from numerous randomized controlled studies provides a high level of proof that, across the different comparator classes, sulfonylureas are safe in terms of total and cardiovascular mortality. That gliclazide, in particular, is safe was supported by a Danish observational study that compared the cardiovascular risk across the sulfonylureas and showed a reduced cardiovascular risk with gliclazide, and went as far as to suggest a specific protective effect of metformin and gliclazide.

The mechanisms involved could include the previously mentioned greater selectivity of gliclazide for pancreatic—rather than myocardial—sulfonylurea receptors. Alternatively, the fibrinolytic properties of gliclazide, independent of its glucose-lowering action, could confer a greater cardiovascular protection. Furthermore, a lower incidence of hypoglycemia along with weight neutrality have been documented with gliclazide in comparison with other sulfonylureas.

Definitive evidence of gliclazide’s cardiovascular safety comes from the ADVANCE study where for 5 years, 91% of patients in the intensive group received gliclazide MR with 71% at the maximum dose of 120 mg. Whatever the parameter measured, whether it was major cardiovascular events, stroke, myocardial infarction, heart failure resulting in hospitalization or death, all-cause mortality, or cardiovascular death, targeting more intensive glucose lowering with a gliclazide MR–based strategy showed absolutely no evidence of harm. There was even a 12% numerical trend for a reduction in the risk of cardiovascular death, unlike any of the recent DPP-4 inhibitor outcome studies despite their being designed and powered for superiority.

Cardiovascular safety

Although data on cardiovascular morbidity and mortality during treatment with sulfonylureas are contrasting, a meta-analysis of 62 randomized clinical trials reporting major cardiovascular events with sulfonylureas versus various comparators detected no signal for cardiovascular risk, with an overall odds ratio (OR) for major cardiovascular events with sulfonylurea treatment versus comparators of 1.08 (95% CI, 0.86-1.36).

Data do suggest, however, that different sulfonylureas might have a different impact on morbidity and mortality. A population-based case-control study showed a significantly increased risk of myocardial infarction in subjects using glibenclamide, but not gliclazide or glimepiride. Among patients with type 2 diabetes receiving combinations of metformin and sulfonylureas, a significantly higher all-cause mortality was observed in those treated with glibenclamide in comparison with gliclazide. A retrospective analysis of 21,325 patients with type 2 diabetes followed over 5.5 years found that gliclazide was associated with a significantly reduced risk of acute coronary syndrome-related hospitalization compared with glibenclamide.

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Renal benefits
Given the major role of hyperglycemia in the development of microvascular complications, reducing blood glucose plays a critical role in their prevention. Large randomized controlled trials have demonstrated a reduction in microvascular complications with intensive glycemic control. Extra attention, however, is needed for kidney protection because reduced kidney function and albuminuria increase the risk of cardiovascular morbidity, kidney failure, and mortality.

Diabetic nephropathy, a common microvascular complication of diabetes caused by damage secondary to hyperglycemia in small blood vessels, is one of the most significant long-term complications in terms of morbidity and mortality for individual patients with diabetes, and is the single most common cause of end-stage renal disease (ESRD) in adults in western countries. Over the last decades there has been a dramatic increase in the proportion of ESRD patients affected by diabetes, and this increase is largely due to type 2 diabetes. Among all patients who started kidney-replacement therapy in 2012, approximately 50% had diabetic kidney disease. The incidence of chronic kidney impairment is expected to increase in the future, because type 2 diabetes is developing at an increasingly younger age and life expectancy has increased due to improved treatment for cardiovascular risk factors.

Intensive glycemic control has been shown to decrease the risk of developing diabetic kidney disease as well as delaying and/or preventing its progression. The benefit of intensive glucose control in the prevention of microalbuminuria has been shown in type 1 diabetes by the DCCT trial (Diabetes Control and Complications Trial) and in its long term follow-up (EDIC). In addition, a recent observational study compared reliable (sustained doubling of serum creatinine levels from baseline) and clinically relevant (new-onset ESRD) long-term kidney outcomes. In a propensity score–matched analysis of patients with type 2 diabetes treated with either glimepiride or gliclazide for a median of 4.7 years, gliclazide offered significant renal protection compared with glimepiride in those patients effectively controlled (HbA1c<7%) on their respective treatment. That is, where glucose lowering is equivalent, the observation of beneficial outcomes for diabetic nephropathy suggests a distinctive renoprotective property of gliclazide above and beyond that of just glucose lowering. Moreover, as with the ADVANCE study, these results confirm that early initiation and maintenance of intensive treatment with gliclazide MR is the optimum strategy for the prevention of major, clinically relevant, complications later on.

Conclusions
Treatment of type 2 diabetes needs to address disease progression and balance the pharmacological efforts that lower hyperglycemia against the increased risks of hypoglycemia and weight gain. As patients with type 2 diabetes experience increased risk of cardiovascular morbidity and mortality over...
time, treatment strategies should ideally address cardiovascular risk factors including body weight, blood pressure, dyslipidemia, and renal function. Decreased mortality and decreased macrovascular and diabetes-related endpoints have been demonstrated in patients using metformin from the time of the diagnosis, supporting it as the first choice of oral blood glucose–lowering medicine. Medical treatment generally follows a stepwise approach, and while therapy may be initiated with metformin, if the HbA1c target is not achieved, international guidelines recognize that sulfonylureas are easy to administer, are low in cost, and are among the most potent of all oral antidiabetics. However, when selecting a treatment, clinicians need to consider the differences in risk.

Gliclazide MR has been shown to effectively lower HbA1c, with sustained glycemic control alongside an optimal safety profile in terms of weight gain and hypoglycemia (lowest risk of any sulfonylurea and comparable to that of a DPP-4 inhibitor). Gliclazide MR–based intensive glucose control is the only therapeutic strategy to significantly reduce the incidence of clinically relevant renal complications and is thus effective in delaying and/or preventing the long process of diabetic kidney disease. In view of gliclazide’s complete cardiovascular safety and unmatched clinical evidence of benefits, the recent Dutch type 2 diabetes management guidelines specifically recommend gliclazide (rather than sulfonylureas as a class) as a preferred second treatment option.

References


Bénéfices basés sur les preuves d’un sécrétagogue sélectif : Diamicron LM 60 mg

La prise en charge du diabète de type 2 nécessite de s’occuper à la fois de la progression de la maladie et de maintenir un équilibre entre les efforts pharmacologiques visant à diminuer l’hyperglycémie et l’accroissement des risques d’hypoglycémie et de prise de poids. De plus, le risque de morbi-mortalité cardio-vasculaire des diabétiques de type 2 étant plus élevé, les stratégies thérapeutiques doivent s’intéresser non seulement à la diminution de l’hyperglycémie, ce qui réduit le risque de complications microvasculaires et probablement aussi macrovasculaires, mais aussi, au contrôle des autres facteurs de risque cardio-vasculaire et à l’amélioration de l’hygiène de vie. Certaines données montrent que les bénéfices sont meilleurs avec un contrôle intensif de la glycémie au plus tôt au cours de la vie des patients. Le gliclazide à libération modifiée (gliclazide LM) a démontré son efficacité en termes de baisse d’HbA1c avec un contrôle glycémique qui se maintient dans le temps. En plus de son efficacité hypoglycémiantne, il a montré une diminution significative de l’incidence des complications rénales cliniquement pertinentes avec un risque d’hypoglycémie et de mortalité cardio-vasculaire le plus faible parmi les sulfonylurées. Au regard de son rapport bénéfices/risques favorable et de ses bénéfices cardio-vasculaires potentiels, les recommandations hollandaises de prise en charge du diabète de type 2 viennent de reconnaître le gliclazide (plutôt que la classe des sulfonylurées) comme traitement de choix de seconde ligne.
Diabetes self-management relies on the patient’s ability to perform a complex self-care routine that includes monitoring blood glucose, taking medication, making healthy dietary choices, and participating in regular physical activity. Effective communication between patients and care providers is critical to achieving positive health outcomes. Beyond the patient-provider perception gap, diabetes self-management support among high-risk patients entails considering together the contextual heterogeneity of patients, the chronic and long-term dimension of self-management, the organizational aspects of care and support, and the health literacy profiles as well as responses to people’s health literacy needs. Adherence to preventive care results from the adaptive trajectories of patients who seek explanations, legitimization, ways to cope with therapeutic measures, access to information, but also from education and services through interactions with trusted caregivers and professionals.

The communication skills of health professionals are key to responding to patients’ needs. Openness, active listening, timely advancement, and respect for the singular trajectory of each individual patient are crucial in helping patients self-manage the disease. Health professionals must focus primarily on the patient rather than on medical considerations, pathophysiology, or even the disease itself. The patient needs to trust and rely on an expert professional, but he/she must also be allowed to proceed at his/her own pace. It must be kept in mind that self-management ed-

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Interview with X. Debussche, France

Diabetes is a chronic disease. As such, it needs to be managed from a long-term, preventive, and integrative perspective. Chronic disease management is a durable constraint that demands coping skills on the part of patients. Patients and health-care professionals do not share the same perception of the disease, for the latter is both eminently social and pathophysiological. Moreover, this perception gap persists even in the case of demographic or cultural proximity. Most health professionals oppose rational, normative biomedical recommendations to meaningful individual stories, interpretations, and experiences. Yet long-term disease management relies not only on evidence-based facts, but also on individual, social, and contextual elements as part of a shared decision process between patient and health professionals.

How can we reduce the gap in perception of diabetes care concepts between patients and providers

The person with diabetes is at the center of a whole support and educational process. He/she is in charge of carrying out the hard work of managing his/her illness day by day. The role of caregivers and educators is to make this work feasible and easier. The primary objective of self-management education intervention or action is to provide individuals with the items, resources, and means that will enable them to progress in their own manner, in the long—or at least the short or medium—term.”

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ucation (SME) is primarily aimed at maintaining and improving patients’ health and quality of life. The danger of focusing primarily on behavioral changes during the medical encounter lies in directly linking behavior to biomedical indicators. This may result in patients’ defensive reactions towards health professionals, and hence in the negotiation of responsibility rather than in the consideration of patients’ health practices. The person with diabetes is at the center of a whole support and educational process. He/she is in charge of carrying out the hard work of managing his/her illness day by day. The role of caregivers and educators is to make this work feasible and easier. The primary objective of SME intervention or action is to provide individuals with the items, resources, and means that will enable them to progress in their own manner, in the long—or at least the short or medium—term.

What additional measures must be taken with high-risk populations presenting specific barriers to diabetes management (eg, the elderly, the economically disadvantaged, or cultural minorities)?

Specific measures must be implemented with high-risk populations; this can prove demanding for relatives, health professionals, and health-care structures and teams. Four key items can be individualized: the contextualization of SME; the long-term and chronic dimension of self-management; the health literacy of people with diabetes; and the organizational aspects of health and care systems and facilities.

**Contextualization of self-management education**

Whenever possible, SME should encourage the expression of individuals’ social and cultural microcontexts, and take into account the advantages and constraints of patients’ environment. The educational encounter rarely takes place in the ordinary contexts in which an individual’s health is threatened. Still, it seems necessary to negotiate the properties of the environment in which any action is to be implemented. For chronic diseases, the individual must cope with the uncertainty of the “why” and, especially from a medical point of view, with what directly affects his/her life: symptoms, treatments with uncertain effects, and hypothetical durations. Thus, in an SME situation, patients’ sociocultural and “ordinary” contexts should, as far as possible, be rendered legitimate, visible, and/or manageable (through photographs, prints, diagrams, flyers, medication boxes, material, food, etc). The means deployed to achieve this must be adapted to the heterogeneity of the cultural environment, and must represent the diversity of the population (housing, food, clothing, religion, languages, etc). The learner-patient may continue to handle and develop his/her own context and environment, identifying difficulties, facilities, barriers, resources, supports, etc, through his/her practical experiences. The role of peers (or expert patients) ought to be stressed here. It can be considered in terms of experiential and contextual development, thus creating and promoting a space for decision-making and taking into account complex interactions beyond the single patient-caregiver relationship.

**Chronic dimension of self-management**

SME must integrate both the duration of the chronic disease and the need to consider actions over the long term. The decision-making process is personal, but is then confronted with daily social interactions. Indeed, decision-making is potentially scalable, unified, and not subjected to the judgments or the authority of health professional(s). The long-term “work” of patients constitutes the central challenge. The decision behind an action remains the patient’s property, even as it is encouraged by the caregiver or educator to improve the patient’s psychosocial skills. The continuities and disruptions of the patient’s trajectory have to be acknowledged by healthcare teams. Whatever the disruptions, health professionals and resources remain crucial to this trajectory.

**Health literacy**

Health literacy refers to the characteristics and social resources needed for people to access, understand, use, and appraise information in order to make decisions about their health. In several studies, lower functional health literacy scores, measured as reading ability and numeracy, have been shown to be associated with higher avoidable hospitalization rates, decreased ability to self-care, and poorer health outcomes. Beyond functional literacy and numeracy skills, health literacy includes: (i) interactive skills (cognitive and social skills to participate actively in daily activities, apply new information to changing circumstances, extract information, and deduce the meaning of different forms of communication); and (ii) critical skills (analysis of critical information and use of this information to better control life events and situations), which are often largely overlooked. Health literacy tools must integrate the measurement of ability to engage with health-care providers, navigate the health system, or critique health information. Instruments like the Health Literacy Questionnaire, which explores 9 domains of health literacy via 44 items, has been developed in several languages and is a useful tool for healthcare teams and structures.

**Organizational aspects**

SME should be considered in its eminently social dimension. Three levels of action can be individualized: microsituational (the educational encounter: patient-caregiver relationship, individual session, educational group); mesocontextual (health professionals, teams, structures, and facilities); and macrocontextual (health policy context; recommendations; community in its religious, cultural, linguistic, and economic dimensions). At the microsituational level, team resources, potentialities, and advances are key to the progress of health professionals.
But patient trajectories must also be given a space of freedom, even if this results in nonadherence to educational actions themselves. The need for structuring may interfere with the heterogeneity of patient pathways. Objective-based programmes (tailored interventions, action plans) may reach their limits here in terms of patient self-management and support. SME sessions and programmes must be better developed and outlined beforehand by multidisciplinary health-care teams.

At the mesocontextual level, the continuity of the care process across health structures, facilities, and professionals is most often lacking, or else reduced to its simplest form. Chronically underserved patients need easy access to medical, educational, social, or psychological expert professionals. The German Diabetes Management study in Germany and the Chronic Care Model study in the US have shown encouraging results by integrating the primary care physician at the core of the care process. However, these formalized systems may have the perverse effect of rendering dominant the expertise of practitioners, without really responding to the expectations of patients, who then become passive subjects “under supervision.” The effects of new organizational implementation have yet to be determined in the context of SME.

To become active partners, patients need easy and flexible access to trusted and expert professionals who respect both their knowledge/opinions about their disease and their preferences. If this accessibility and the visibility thereof are lacking, patients’ needs will be expressed in emergencies, which provide medical and social assistance, in particular to the poorest. Health (and social) system simplification, coordination, and visibility are essential to ensure real access and synchronization between self-care and support from professionals.

At the macrocontextual—institutional and political—level, the challenge of chronic disease requires a multifaceted response to trajectories, needs, and complex contexts. Overall, existing interventions and organizations only modestly impact the health of chronic patients and the access to and use of adequate services. Overly strict recommendations or uniform structuration may conceal the need for individual and social work on individual trajectories. Programme and curriculum structuring is important in itself, but its effects remain unclear and poorly known. An important research initiative has yet to be developed on these issues. Approaches must integrate patients, professionals, and health system organizations to better reflect the needs generated by the chronic disease. Assessment of health literacy needs can guide the implementation of specific responses, such as the one developed in Australia through the Ophelia program.

What is patients’ perception of risk and risk assessment, and how are diabetes risk assessment tools implemented in practice?

How can patients’ perception of treatment burden lead to adherence and to subsequent net benefits in terms of glycated hemoglobin?

The chronic and progressive nature of the disease is underestimated, and diabetes complications are not well known by most people with diabetes, whatever the duration of the disease. People with low educational levels or low literacy skills cite complications less frequently. Patients with diabetes generally do not consider themselves sick until pain or complications actually occur. The notion of disease as a medical concept does not correspond to the condition of diabetes. Diabetes is not really considered a disease like any other: it is a long-lasting and silent illness, potentially serious, but hard to understand and describe. Despite its seriousness, it is usually taken into consideration very slowly. In fact, individual progress from diagnosis to patent disease and complications is remote from the biomedical process.

Risk assessment for the prevention of complications is for the most part poorly understood by patients. Several risk assessment tools have been developed; yet they are seldom used by physicians in everyday medical practice. The objective of these tools is to guide health professionals in determining the level of treatment intensification. But they could also be useful tools to help patients self-manage the disease and cope with self-care preventive activities via risk communication strategies. Individuals need to better understand the multiplicity of risk factors. Risk information can improve accuracy of risk perception as well as increase the intention to initiate prevention strategies.

In SME interventions aimed at preventing complications through risk assessment, subjects have to look at health and well-being, as well as disease risk. Modifiable (rather than nonmodifiable) elements must be mobilized and worked on by patients (blood glucose and glycated hemoglobin, blood pressure, lipids, weight and body mass index, waist circumference, smoking, etc), and actions that may have a positive effect on these elements have to be identified, analyzed, and compared (physical activity/inactivity, diet, medication, etc). Before realistic actions can be decided upon, this work has to be completed by confronting the elements of real life: social environment, cultural embeddedness, financial resources, social and familial support, stress, geographic context, medical and allied support, etc.

Adherence to treatment means far more than medication, diet, and exercise compliance. While treatment goals in diabetes mainly relate to maintaining a correct glycemic level, patients identify a variety of constraints that influence treatment—including work, financial aspects, and constraints related to housing, family, dependents, insecurity and financial difficulties, gender roles, etc. Chronic patients must manage the disease (symptoms, diagnosis,
management of “events,” everyday life, and the “biographical work” necessary to rebuild their identity. At the onset of disease, they need and seek explanations and legitimization, but are rapidly confronted with the impact of the therapeutic process. Hence, they have to develop adaptive resources through coping skills (tolerating the effects of the disease and maintaining self-confidence), strategy (alleviating the effects of the disease), and style (responding to the disease and to therapeutic procedures, for example by isolating themselves or by emphasizing the illness as a component of their social identity). As part of self-care activities, individuals look for a correct balance between health and well-being. When the search for better health does not affect well-being, adherence to dietary and medical advice is not a problem.

Beyond the difficulties associated with the adverse events and effectiveness of the drug, nonadherence is in line with a process of self-regulation that includes testing, the control of dependence, destigmatization, and the development of a “pragmatic practice.” Social and family support is important for the chronic patient, although it may have ambivalent effects on the development of individual strategies for coping with the disease. Most patients are, in fact, fully aware of medical recommendations in terms of diet, physical activity, self-monitoring, and treatment. The importance of understanding the complex factors involved in human experience and their relation to diabetes management has been highlighted in the case of ethnic or cultural minorities, for whom structural and material barriers—as opposed to beliefs and behaviors, as is usually suggested—are the most important factors in explaining poor adherence. Finally, multiple medications or the occurrence of comorbidities often raise doubts about the safety of the drug mix and about the complexity of drug-specific instructions. In this context, the individual’s position and suspicion towards the medical professions in general, and towards pharmaceutical companies in particular, may have an impact. The nonanticipated chronic dimension of the illness may cause frustration and suspicion of treatment ineffectiveness (or that the effects of treatment are potentially more deleterious than beneficial), leading to distrust of medical discourses in general.

The concept of adherence can thus be considered from a perspective that gives full significance to patients’ heterogeneous trajectories and therapeutic strategies, but also to medical explanations of the disease, to social interactions and contexts, to ownership and understanding of the mechanisms and phenomena involved, and to the relational and organizational aspects of the health system. Developing and structuring SME actions will benefit from integrating the complexity of these various trajectories and interactions.

References

Keywords: adherence; diabetes; high-risk population; perception; risk assessment; self-management education;
Approximately 382 million people worldwide are affected by type 2 diabetes mellitus (T2DM) making it the most common form of diabetes. Its prevalence in elderly subjects is greater than that in the younger population, and it has been attracting increasing attention because of its disabling complications and the co-occurrence of other chronic conditions. High glucose levels can damage nerves and blood vessels leading to multiple diabetic complications, such as retinopathy, nephropathy, peripheral neuropathy, and vascular diseases. An increasing number of studies have shown that diabetes is also a risk factor for both vascular dementia and Alzheimer’s disease and that it may accelerate the progression from mild cognitive impairment (MCI) to dementia. It has, in fact, been found that T2DM is associated with poor performance in cognitive tasks involving attention, executive functions, episodic memory, psychomotor speed, and visual-constructive skills in persons without dementia. Preclinical studies in animals have demonstrated that some antidiabetic drugs can have an effect on brain metabolism, neuroinflammation, and neuroregeneration, which indicates that these drugs could be also used to treat major neurodegenerative diseases, such as Alzheimer’s disease. Several clinical trials are now underway to assess their efficacy in MCI and in the early stages of Alzheimer’s disease.

Medicographia. 2016;38:92-97 (see French abstract on page 97)

Type 2 diabetes mellitus (T2DM) is one of the most common chronic conditions in the world. Its prevalence rate increases sharply with age, rising from about 3% in individuals between 20-39 years to rates between 12% and 25% in those 65 years and over; in recent years, the largest increase has been noted in the oldest age groups. The general trend being seen in both developed and developing countries is that of an increasing prevalence of prediabetes and diabetes linked to increments in obesity, mostly due to a modern sedentary lifestyle. It is predicted that by 2035, the number of patients with diabetes will increase by over 50%, from 382 million individuals today to 592 million. Many cases of T2DM could be prevented through appropriate lifestyle strategies, such as participating in a physical exercise program, losing weight, or following a healthy diet. Once diagnosed with T2DM, patients can be treated with diet, oral hypoglycemic agents, or insulin.

Alzheimer’s disease is the most common form of dementia and constitutes one of the most pressing problems challenging health-care systems. The number of persons affected with dementia worldwide today is estimated to be approximately 35.6
million; that number is predicted to almost double by 2030 and to more than triple by 2050. Alzheimer’s disease is characterized by the cortical accumulation of β-amyloid plaques and neurofibrillary tangles, which are aggregates of hyperphosphorylated τ protein, responsible for the neuroinflammation and the oxidative stress that lead to brain atrophy and widespread synaptic and neuronal loss.

Given the magnitude of the phenomenon, its social and clinical implications, and the fact that there is at yet no effective cure, it is of the upmost importance to reduce the risk of dementia or to delay its onset.

T2DM causes accelerated aging in most organ systems and severe complications, such as nephropathy, coronary artery disease, peripheral artery disease, blindness, and peripheral neuropathy; T2DM’s effect on the central nervous system (CNS) has been clearly delineated, and it has been identified as an independent risk factor for cognitive decline and for vascular and neurodegenerative dementia. T2DM is also associated with poor performance in cognitive tasks involving attention, executive functions, episodic memory, psychomotor speed, and visual-constructive skills in individuals without dementia. Minor diabetes-associated cognitive decrements seem to affect all age groups, tend to progress slowly over time, and could reduce the threshold at which the process of dementia becomes symptomatic in older individuals. While T2DM’s association with vascular dementia seems straightforward in view of the fact that the vascular system, including the cerebrovascular sector, is damaged by hyperglycemia, its association with neurodegenerative conditions continues to be unclear. The epidemiological evidence and the biological plausibility of the association between T2DM and Alzheimer’s disease, as well as the potential benefits of the treatment of T2DM in preventing neurodegeneration, are outlined below.

Is there any epidemiological evidence of an association between T2DM and Alzheimer’s disease?

Given the many risks and confounding factors involved in the association between T2DM and dementia, a causal association between the two is difficult to establish. Moreover, dementia is more likely to be present when vascular and Alzheimer’s disease lesions coexist, a situation that is especially common with increasing age, when mixed dementia cases are the ones most commonly found in the population. Potential risk factors include diabetes-specific characteristics (hyperglycemia, hypoglycemia, endothelial dysfunction, inflammation, and micro- or macrovascular complications). Longitudinal studies focusing on changes in cognitive functions over time are the best way to establish a causal relation. Some longitudinal studies have attempted to identify specific cognitive deficits using batteries of neuropsychological tests and the Mini Mental State Examination. Several population-based longitudinal studies have demonstrated that diabetics have an increased risk of stroke and vascular dementia, although some studies have also reported an increased risk of neurodegenerative forms of dementia, in particular Alzheimer’s disease.

A recent meta-analysis on T2DM and dementia risk6 examining data from 19 published studies including 6184 patients with T2DM and 38350 controls found a relative risk for vascular dementia at 2.48 (95% confidence interval [CI], 2.08-2.96) and a relative risk for Alzheimer’s disease at 1.46 (95% CI, 1.20-1.77).

<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>Vascular dementia</th>
<th>Alzheimer’s disease</th>
<th>Progression from mild cognitive impairment to Alzheimer’s disease</th>
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<tr>
<td>Cheng, 20128</td>
<td>2.48 (95% CI 2.08-2.96)</td>
<td>1.46 (95% CI 1.20-1.77)</td>
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<tr>
<td>Li, 20159</td>
<td>-</td>
<td>-</td>
<td>1.52 (95% CI 1.2-1.91)</td>
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The relationship between T2DM and mild cognitive impairment (MCI), considered an intermediate stage characterized by selective impairments on cognitive testing, but normal performance in activities of daily living, is particularly interesting. It has been seen that 10% to 15% of MCI cases progress to overt Alzheimer’s disease in the subsequent year. A recent meta-analysis analyzing 60 cohort studies including 14821 participants from 16 countries sought to identify the risk factors for predicting the progression from MCI to dementia. T2DM patients with MCI were found to have a relative risk of progression to Alzheimer’s disease of 1.52 (95% CI 1.2-1.91) and—out of all cardiovascular risk factors assessed—T2DM was the only independent predictor of progression from MCI to dementia (Table I).

As the high prevalence of diabetes makes it potentially one of the most important modifiable risk factors for Alzheimer’s disease, clinicians and researchers are exerting every effort to decrease the prevalence of T2DM and to control its progression, with a view to preventing Alzheimer’s disease and learning more about the potential CNS benefits of selected anti-diabetic drugs.
Is there a plausible biological mechanism for Alzheimer’s disease development in T2DM?

The pathophysiological mechanism linking T2DM and Alzheimer’s disease is still obscure. A common genetic predisposition to both T2DM and Alzheimer’s disease could explain, at least in part, the link. However, it is quite probable that vascular factors, hyperinsulinemia, dyslipidemia, and hypertension also play a role. The fact that the elderly are more susceptible than younger subjects to the effects of T2DM on cognitive function indicates that the disease interacts with or accelerates the process of cerebral aging. Changes in the CNS observed in T2DM patients are very similar to those characterizing aging, and neuropsychological testing has confirmed this hypothesis: patients with T2DM, in fact, show a decline in verbal memory and information processing velocity, alterations which are typical of changes associated with aging. Pathogenetic factors involved in cognitive deficits in T2DM include hyperglycemia and increased production of advanced glycation end products (AGEs), which damage the vascular system and endothelial functions and lead to inflammatory reactions and amyloid deposition. In rat experimental models, treatment with AGEs induces hyperphosphorylation and impairs synapse and memory through upregulation of the AGE receptor. Hyperglycemia may also affect blood flow to the brain, neurotransmitter functions, and the supply of nutrients to the brain, thus causing cerebral neurodegeneration. Hyperinsulinemia also seems to contribute to the development of Alzheimer’s disease in type 2 diabetes mellitus. Insulin crosses the blood-brain barrier, and insulin receptors are present in the hippocampus and several other areas of the brain. Insulin-degrading enzyme breaks down amyloid β and, in cases of insulin resistance, the increased concentration of insulin that occurs means that competition from insulin for binding sites of this enzyme may reduce the clearance of amyloid β. As many of the abnormalities attributable to insulin resistance seen in T2DM at the cellular level, including inflammation, metabolic stress, mitochondrial dysfunction, and endoplasmic reticulum stress, are also observed in Alzheimer’s disease, Alzheimer’s disease is often referred as type 3 diabetes.

Brain imaging reveals that T2DM is associated with brain atrophy that only slightly exceeds the expected age-related brain volume reduction: lacunar infarcts occur approximately twice as often in T2DM, and alterations in structural and functional connectivity have been identified as possible brain imaging markers of T2DM.

Is there any evidence that we can decrease the risk of Alzheimer’s disease by treating T2DM?

As diabetes might increase the risk of dementia by affecting the amyloid cascade and by means of vascular complications, investigators have begun to wonder if tight glycemic control could prevent dementia. It has been hypothesized that patients with T2DM and MCI or mild Alzheimer’s disease might benefit from pharmacological treatment for diabetes because at these stages, T2DM is still a risk factor for progression of cognitive decline. When dementia is at more advanced stages, diabetes-specific treatment would no longer, hypothetically, affect its progression. As diabetes complications, such as retinopathy, diabetic foot, microvascular complications, and cerebrovascular and cardiovascular diseases, are all associated with an increased risk of dementia, tighter glycemic control should, in principle, reduce the risk of dementia. Findings from large clinical trials have not, however, provided fully convincing results. The ACCORD-MIND (Action to Control Cardiovascular Risk in Diabetes–Memory in Diabetes) trial showed that patients with diabetes and high cardiovascular risk who were randomized to tighter than normal glycemic control had a cognitive performance that was similar to that in controls receiving standard care after 40 months and their magnetic resonance imaging (MRI) scans showed a nonsignificantly lower level of brain atrophy. The Health ABC (Health, Aging, and Body Composition) study found a twofold increased risk for developing dementia in the participants who experienced hypoglycemic events and a threefold increased risk of having a subsequent hypoglycemic event in those who developed dementia. This finding underlines the bidirectional association between hypoglycemia and dementia. The risk-benefit ratio of tight glycemic control is, in any case, less favorable in T2DM patients with cognitive impairment, in view of their risk of hypoglycemia, which in turn increases the risk of cognitive decline. All of these variables need to be considered by a physician entrusted with the care and management of elderly diabetics, who also need to be monitored for MCI and the initial phases of dementia.

Treating cardiovascular complications and hypertension in T2DM patients using statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers might decrease the risk of dementia and thus be an effective preventive strategy. The use of different hypoglycemic agents and insulin remains controversial. The choice of different drugs to treat T2DM is often determined by the severity of the disease and

**FOCUS**

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**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ACCORD-MIND</td>
<td>Action to Control Cardiovascular Risk in Diabetes–Memory in Diabetes</td>
</tr>
<tr>
<td>AGE</td>
<td>advanced glycation end product</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>DPP-4</td>
<td>dipeptidyl peptidase 4</td>
</tr>
<tr>
<td>GLP-1</td>
<td>glucagon-like peptide 1</td>
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<tr>
<td>Health ABC</td>
<td>Health, Aging, and Body Composition</td>
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<tr>
<td>MCI</td>
<td>mild cognitive impairment</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>SNIFF</td>
<td>Study of Nasal Insulin in the Fight against Forgetfulness</td>
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<tr>
<td>T2DM</td>
<td>type 2 diabetes mellitus</td>
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this factor, more than the drug itself, may account for differences noted in Alzheimer’s disease risk. However, in view of common mechanisms shared by T2DM and Alzheimer’s disease, antidiabetic drugs might indeed positively affect brain-cell metabolism. Table II presents the potential impact of particular antidiabetic treatments on the CNS.


- Increased neuroprotection
- Increased synaptic plasticity
- Increased neurogenesis and gliogenesis
- Increased insulin sensitivity
- Increased mitochondrial function
- Decreased neuroinflammation

Table II. Potential beneficial central nervous system (CNS) effects of antidiabetic drugs (insulin, metformin, sulfonylureas, thiazolidinediones, glucagon-like peptide 1 [GLP-1] agonists, dipeptidyl-4 [DPP-4] inhibitors).

**Insulin**

Growing evidence has shown that insulin has multiple functions in the brain, and that its dysregulation may contribute to the pathogenesis of Alzheimer’s disease. However, the risk of hypoglycemia associated with peripherally-administered insulin as a treatment for Alzheimer’s disease makes this approach unsuitable, but it has been demonstrated that administering insulin directly to the brain of animals can recover unsuitable, but it has been demonstrated that administering insulin directly to the brain of animals can recover

**Sulfonylureas**

Sulfonylureas may protect against neurodegeneration by preventing neurofibrillary tangle formation, increasing the brain’s antioxidant capacity, and preventing inflammation. Indeed, glibenclamide has been shown to reduce hyperphosphorylated τ protein levels and lipid peroxidation in rats’ brains, while glipizide seems to reduce the total oxidant index and increase total antioxidant defence in the brain.25

As results in humans are contradictory,27,29 long-term longitudinal studies on these agents, perhaps in combination with other drugs, are required to verify their therapeutic efficacy.

**Thiazolidinediones**

Rosiglitazone and pioglitazone are both potent insulin sensitizers that work by activating peroxisome proliferator-activating receptor γ (PPAR-γ), but the former has been withdrawn from the market because it was shown to have negative cardiovascular disease effects. Pioglitazone is now widely used, although at high doses it also might cause negative effects, such as bone fractures and bladder cancers.30 While preliminary studies have not shown significant benefits in patients with mild Alzheimer’s disease, it is possible that the neurodegeneration was too advanced to allow any potential benefit from the drug.

A multicenter trial is currently ongoing in 50 centers worldwide, with two goals: (i) to verify if a new genetic risk algorithm comprising apolipoprotein E (APOE) and TOMM40 genotypes can determine if participants are at risk of developing MCI due to Alzheimer’s disease within the next five years; and (ii) to evaluate if pioglitazone is able to delay the onset of MCI due to Alzheimer’s disease in cognitively normal individuals who are at high risk of developing MCI due to Alzheimer’s disease, as identified by the biomarker risk algorithm. The results will be available in 2019.

**Glucagon-like peptide receptor 1 agonists and dipeptidyl peptidase 4 inhibitors**

Two drug classes have been developed more recently: glucagon-like peptide 1 (GLP-1) receptor agonists and dipeptidyl peptidase 4 (DPP-4) inhibitors. Clinical data have revealed that these agents improve glycemic control while reducing body weight (GLP-1 receptor agonists, specifically) and systolic blood pressure in patients with type 2 diabetes. Furthermore, the incidence of hypoglycemia is lower with these treatments because of their glucose-dependent mechanism of action.

Due to the rapid degradation of GLP-1, several more stable analogues have been generated, the most recent being lixivatinide, which reduces peripheral insulin resistance, has an excellent safety profile, and is accompanied by a low incidence of hypoglycemia during chronic administration.31,32 These drugs have also been shown to have a neuroprotective effect,33 as they promote the formation of new synapses...
and neurogenesis and protect against oxidative injury. In mice, they have been shown to lower β-amyloid and tau protein levels, leading to reduced inflammation and improved cognition. Two important clinical trials are currently ongoing: one to determine the safety and tolerability of exendin-4, as well as to acquire preliminary evidence for its effectiveness administered twice daily, as a treatment for early-stage of Alzheimer’s disease and MCI; the other is a 12-month, multicenter, randomized, double-blind, placebo-controlled phase 2b study in patients with mild Alzheimer’s dementia, which is being carried out to test the effect of liraglutide on cerebral glucose utilization, cognition, structural and functional MRI, and cerebrospinal fluid biomarkers.

DPP-4 is the enzyme that degrades GLP-1, so by inhibiting this enzyme the DPP-4 inhibitors stabilize the level of GLP-1. Saxagliptin, sitagliptin, and vildagliptin have all been proven to reduce amyloid burden, phosphorylation, and inflammation and in improving cognition in rats. Further studies comparing these drugs with the GLP-1 agonists, perhaps in combination with other antidiabetic drugs, are required to determine their impact in human cognition.

◆ Other drugs

Other antidiabetic drugs may be of interest for their potential neuroprotective actions. In particular, amylin, a hormone secreted from pancreatic β cells, like insulin, plays a role in glycemic regulation by delaying gastric emptying and promoting satiety, thereby preventing postprandial spikes in glycemia. It passes through the blood-brain barrier easily and mediates brain functions, including inhibiting appetite to improve glucose metabolism, and probably enhances neural regeneration. However, amylin tends to aggregate in oligomers and fibrils in the pancreas, leading to β-cell dysfunction and reduced insulin secretion. A recent study found an accumulation of amylin amyloid in the cerebrovascular system in an Alzheimer’s disease brain; abundant amylin β in an Alzheimer’s disease brain may block the ability of amylin to bind to its receptor and hinder normal amylin functions that are essential for the brain. A soluble, nonaggregating analogue, pramlintide, has been developed to be used with insulin in the treatment of diabetes and, recently, it was found to be effective in reducing β-amyloid burden and improving cognition in Alzheimer’s disease transgenic mice, as well as in increasing synaptogenesis and reducing oxidative stress and neuroinflammation. Studies in humans are expected in the near future.

Conclusions

The risk of Alzheimer’s disease is significantly increased in T2DM, although the risk for vascular dementia is even higher. Vascular risk factors might explain, in part, the association with Alzheimer’s disease, but other mechanisms directly affecting the neurodegeneration typical of Alzheimer’s disease also exist. Insulin resistance, which is the hallmark of T2DM, seems to play an important role also in Alzheimer’s disease. Some drugs that improve insulin sensitivity can also act in the brain to promote brain energy metabolism, neuronal survival, and synaptic plasticity. These drugs reduce neuroinflammation and might also increase neurogenesis and brain repair processes. Ongoing clinical trials are assessing their efficacy in preventing the progression of MCI and Alzheimer’s disease in humans. Randomized clinical trials are also needed to assess if improved diabetes control leads to a lower incidence of Alzheimer’s disease. Meanwhile, the dramatic increase in the prevalence of T2DM and Alzheimer’s disease worldwide implies that there are and will be a greater number of older, cognitively impaired patients, who have difficulty with aspects of diabetes self-management and are, therefore, at higher risk of adverse outcomes, such as hypoglycemia. Clinicians and health-care systems must carefully consider these challenges and envision adequate actions.

References

Le lien entre le diabète de type 2 et la maladie d’Alzheimer

Le diabète de type 2 (DT2) touche environ 382 millions de personnes dans le monde, ce qui en fait la forme la plus répandue de diabète. Sa prévalence est plus importante chez les sujets âgés que chez les plus jeunes ; ses complications invalidantes et sa coexistence avec d’autres maladies chroniques en ont fait un sujet d’intérêt croissant. Une glycémie élevée peut léser les nerfs et les vaisseaux sanguins, entraînant de nombreuses complications diabétiques comme la rétinopathie, la néphropathie, la neuropathie périphérique et les maladies vasculaires. De plus en plus d’études montrent que le diabète est aussi un facteur de risque pour la démence vasculaire et la maladie d’Alzheimer, et qu’il peut accélérer le passage du trouble cognitif léger (TCL) à la démence. En fait, il a été montré que le DT2 est associé à des performances médiocres dans les tâches cognitives impliquant l’attention, les fonctions exécutives, la mémoire épisodique, la vitesse psychomotrice et les qualités visuo-construitives chez les sujets ne souffrant pas de démence. Des études précliniques chez l’animal ont montré que certains antidiabétiques peuvent agir sur le métabolisme cérébral, l’inflammation neuronale et la neurorégénération, ce qui montre que ces médicaments pourraient aussi être utilisés dans le traitement des principales maladies neurodégénératives comme la maladie d’Alzheimer. Plusieurs études cliniques sont actuellement en cours pour évaluer leur efficacité dans le TCL et les stades précoces de la maladie d’Alzheimer.

Keywords: Alzheimer’s disease; antidiabetic drugs; cognitive impairment; dementia; type 2 diabetes

The bridge between type 2 diabetes and Alzheimer’s disease – Maggi and Crepaldi

MEDICOGRAPHIA, Vol 38, No. 1, 2016
Monogenic diabetes accounts for approximately 1% to 5% of diabetes cases in young people, and its incidence has increased in recent decades in parallel with greater awareness and wider availability of genetic testing. It results from one or more defects in a single gene, and has been linked to more than 20 different genes. The two major subtypes are neonatal diabetes mellitus (NDM) and maturity-onset diabetes of the young (MODY). Mutations in the hepatocyte nuclear factor 1α (HNF1A) gene lead to the most common cause of familial autosomal dominant diabetes, while mutations in the glucokinase gene (GCK) are the most common cause of persistent, mild, asymptomatic hyperglycemia in the pediatric population. NDM, which typically presents before the age of 6 months, is most often caused by a mutation in one of three genes: KCNJ11, ABCC8, or INS.

The diagnosis of monogenic diabetes should be suspected in patients with one or more of the following characteristics: (i) diabetes presenting before 6 months of age; (ii) strong family history of diabetes; (iii) negative islet autoantibodies; (iii) low or no insulin requirements 5 years after diagnosis; (iv) absence of clinical features of type 2 diabetes; (v) mild fasting nonprogressive hyperglycemia; (vi) diabetes associated with extrapancreatic features. The diagnosis of monogenic diabetes can significantly impact on the care of the affected individual, by enabling prediction of the disease course and guiding appropriate management. Some forms of MODY are sensitive to sulfonylureas, while mild fasting hyperglycemia due to mutations in GCK is not progressive and does not require treatment.

To date, more than 20 different genetic subtypes of monogenic diabetes have been identified, with variable phenotypes and patterns of inheritance. Within families, inheritance may be expressed as a dominant, recessive, or non-Mendelian trait or may present as a de novo mutation. The genetic diagnosis has important clinical implications, because it can significantly impact on management of the affected individual, enabling prediction of the disease course and guiding appropriate therapy.
Implications, because it can significantly impact on management of the affected individual, enabling prediction of the disease course and guiding appropriate therapy.

Epidemiology of monogenic diabetes

Monogenic diabetes represents approximately 1% to 5% of pediatric diabetes cases, although case ascertainment depends on awareness of the potential diagnosis and availability of genetic testing. While most children with genetically proven monogenic diabetes were previously misdiagnosed as having type 1, or less frequently, type 2 diabetes, increased awareness and availability of genetic testing is likely to have improved diagnosis and, therefore, the accuracy of more recent prevalence estimates.

Among adults, there is a relative paucity of data examining the epidemiology of monogenic diabetes. In a UK survey of young adults diagnosed with diabetes before the age of 45 years, the proportion with MODY (3%) was similar to pediatric studies. All had mutations in the hepatocyte nuclear factor 1α (HNF1A) gene (HNF1A-MODY), suggesting a population prevalence of 84 cases per million (95% confidence interval [CI], 31-136). The authors extrapolated that there were at least 5000 cases of HNF1A-MODY in the UK, of whom 90% were undiagnosed. In women with gestational diabetes mellitus, the prevalence of mutations in glucokinase (GCK-MODY) is approximately 0.5% to 1%.

When to consider monogenic diabetes

Most cases of monogenic diabetes present as isolated diabetes, and therefore are commonly misdiagnosed as either type 1 or type 2 diabetes. The diagnosis of monogenic diabetes should be considered in people with diabetes who have an atypical presentation, in particular, if one or more of the following characteristics are present:

- Diabetes presenting before 6 months of age (since type 1 diabetes is extremely rare in this age group);
- Strong family history of diabetes (for example in one parent and other first-degree relatives);
- Diabetes with negative autoantibodies (particularly if measured at diagnosis of diabetes);
- Preserved b-cell function, with low insulin requirements and detectable c-peptide (either in blood or urine) 5 or more years after diagnosis;
- Absence of classical features of type 2 diabetes (obesity, insulin resistance/acanthosis nigricans, high-risk ethnic group);
- Mild fasting, nonprogressive hyperglycemia;
- Diabetes associated with extrapancreatic features (such as renal cysts or deafness)

These characteristics should not be considered in isolation, since the clinical phenotype can vary within and between the various forms of MODY, and there may be overlap with features of type 1 and type 2 diabetes. In particular, while the majority of individuals with MODY are not obese, the presence of obesity does not preclude a diagnosis of MODY. Both obesity and hyperinsulinemia have been observed in people with various forms of MODY.

Classification of monogenic diabetes

The two major forms of monogenic diabetes are neonatal diabetes mellitus (NDM) and maturity-onset diabetes of the young (MODY). The different forms of monogenic diabetes can also be classified according to their main pathogenic mechanisms: genetic defects of pancreatic development, b-cell function, insulin action, and b-cell destruction. The site of action of these mutations localizes to the nucleus, cell membrane, cytoplasm, lysosome, endoplasmic reticulum, or mitochondria. In addition, a variety of genetic syndromes are associated with diabetes or severe insulin resistance (IR). The common forms of monogenic diabetes that typically present during adolescence or adulthood are shown in Table I (page 100); subtypes that present during the neonatal period or infancy are shown in Table III (page 102), and IR syndromes in Table II (page 101). Due to the higher prevalence of MODY compared with NDM, the former will be addressed first.

Maturity-onset diabetes of the young

Three genes are responsible for the majority of MODY cases (GCK, HNF1A, and HNF4A) (Table I), while mutations in a diverse range of genes cause more rare forms of autosomal dominant diabetes. The major MODY subtypes differ by their typical age of onset, glycemic pattern, and treatment. Although most forms are inherited as a dominant trait, sporadic de novo mutations in a number of genes can cause monogenic diabetes.

Glucokinase gene mutations (GCK-MODY, MODY2)

The enzyme glucokinase is the b-cell glucose sensor; it catalyzes glucose phosphorylation (the first step in glycolysis), and therefore has a key role in regulating glucose metabolism. Glucokinase is expressed in the liver and b cells; the rate of glucose metabolism in these tissues is a function of the enzyme’s activity. Heterozygous inactivating mutations in GCK lead to glucokinase deficiency, resulting in an increased
Glucose threshold for insulin secretion and mild nonprogres-
sive hyperglycemia. Although present at birth, hyperglycemia
is often first detected incidentally later in life. Affected indi-
viduals are asymptomatic because the mild hyperglycemia
does not cause osmotic symptoms. It is not uncommon for
a parent or relatives to be undiagnosed or misdiagnosed with
type 2 diabetes.

GCK-MODY is the most common subtype of monogenic di-
abetes in the pediatric population.8 Fasting blood glucose is
typically in the impaired fasting glucose range (5.6-6.9 mmol/
L), and there is usually a small incremental rise in blood glu-
cose (<3.5 mmol/L) during an oral glucose tolerance test
(OGTT).19 Glycated hemoglobin (HbA1c) is mildly elevated but
typically below 7.5%, while free fatty acids (FFAs) are reduced,20
which suggests that there is a compensatory mechanism of
increased insulin sensitivity in the setting of hyperglycemia
and reduced insulin secretion. This contrasts with type 2 di-
abetes, where FFAs are usually elevated. Measurement of
fasting glucose in parents may provide further evidence for
the diagnosis and support genetic testing.

Since the hyperglycemia is mild and not progressive, GCK-
MODY is rarely associated with clinically significant vascular
complications of diabetes.21 Treatment is not required, except
during pregnancy when insulin treatment is recommended if
the fetus does not inherit the GCK mutation.22

HNF1A-MODY (MODY3) and HNF4A-MODY
(MODY1)
Heterozygous mutations in HNF1A are the most common
cause of familial symptomatic monogenic diabetes,3,10,18 while
heterozygous HNF4A mutations are much less frequent. In
both HNF1A- and HNF4A-MODY, impaired glucose tolerance
typically manifests during adolescence or early adulthood.
In the early stages of the disease, fasting blood glucose may
be normal but there is a large incremental rise in blood glu-
cose (>5 mmol/L) after meals or at 2 hours during an OGTT.19
As the disease progresses, patients become symptomatic
(with polyuria, polydipsia) and develop fasting hyperglycemia,
but ketosis is rare due to persistent residual insulin secretion.
People harboring mutations in HNF1A are at high risk of de-
veloping MODY; 63% of heterozygotes will develop diabetes
by age 25 years and the majority (96%) by 55 years.23
Heterozygous individuals with the R76W mutation in
HNF4A can also develop an atypical form of Fanconi renotubular
syndrome: renal cysts or dysplasia; urogenital tract malfor-
mations in females, low fecal elastase

Table I. Classification and clinical features of monogenic diabetes with onset in adolescence or adulthood.
Abbreviations: MODY, maturity onset diabetes of the young; RCAD, renal cysts and diabetes syndrome; Ref, reference.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Inheritance</th>
<th>Clinical features</th>
<th>Ref</th>
</tr>
</thead>
</table>
| HNF4A (MODY1)      | 20q12-q13.1 | Dominant    | Uncommon (~5% of MODY); increased birth weight, macro-
somia, neonatal hypoglycaemia, renal Fanconi renotubular syndrome (mutation specific) | (5) |
| GCK (MODY2)        | 7p15-p13  | Dominant    | Common (30-50% of MODY); no phenotypic features; absence of microvascular and macrovascular complications | (42) |
| HNF1A (MODY3)      | 12q24.2   | Dominant    | Common (30-50% of MODY); low renal threshold for glucose in the early stages of diabetes | (6) |
| IPF1 (MODY4)       | 13q12.2   | Dominant    | Rare (<1% of MODY); variable age of diabetes onset (mean 35 years); obesity, hyperinsulinemia | (43) |
| HNF1B (MODY5)      | 17q12     | Dominant    | Uncommon (~5% of MODY), variable phenotype. RCAD syndrome: renal cysts or dysplasia; urogenital tract malformations in females, low fecal elastase | (44) |
| NEUROD1 (MODY6)    | 2q31.3    | Dominant    | Very rare, adult onset                                                            | (45) |
| KLF11 (MODY7)      | 2p25.1    | Dominant    | Very rare; reduced insulin expression in pancreatic beta cells                      | (46) |
| CEL (MODY8)        | 9q34.13   | Dominant    | Very rare, exocrine (acinac cell) pancreatic dysfunction; lowered fecal elastase     | (47) |
| PAX4 (MODY9)       | 7q32.1    | Dominant    | Very rare, some cases with ketosis prone diabetes                                  | (48) |
| INS (MODY10)       | 11p15.5   | Dominant    | Rare (<1% of MODY); wide clinical spectrum and age of presentation                | (49) |
| BLK (MODY11)       | 8p23.1    | Dominant    | Very rare, obesity common                                                          | (50) |

HNF1A-MODY (MODY3) and HNF4A-MODY
(MODY1)
Heterozygous mutations in HNF1A are the most common
cause of familial symptomatic monogenic diabetes,3,10,18 while
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both HNF1A- and HNF4A-MODY, impaired glucose tolerance
typically manifests during adolescence or early adulthood.
As the disease progresses, patients become symptomatic
(with polyuria, polydipsia) and develop fasting hyperglycemia,
but ketosis is rare due to persistent residual insulin secretion.
People harboring mutations in HNF1A are at high risk of de-
veloping MODY; 63% of heterozygotes will develop diabetes
by age 25 years and the majority (96%) by 55 years.23

Heterozygous individuals with the R76W mutation in
HNF4A can also develop an atypical form of Fanconi renotubular
syndrome: renal cysts or dysplasia; urogenital tract malfor-
mations in females, low fecal elastase

The risk of chronic complications of diabetes is high and related to
glycemic control.25 The frequency of microvascular compli-
cations (retinopathy, nephropathy, neuropathy) is similar to
that of patients with type 1 and type 2 diabetes and HNF1A
mutations are associated with an increased risk of cardio-
vascular mortality.26 Patients with MODY due to HNF1A and
HNF4A mutations can be treated with dietary modification
initially although they will ultimately require pharmacological treatment as their glycerol control deteriorates over time. Sulfonylureas are the first-line treatment, because they can be commenced at a low dose (one-quarter of the normal starting dose in adults) to avoid hypoglycemia. Provided they do not develop significant hypoglycemia, patients can be maintained on low-dose sulfonylureas for decades.27 A recent randomized controlled trial comparing a glucagon-like peptide (GLP-1) agonist with a sulfonylurea demonstrated lower fasting glucose in those treated with the GLP-1 agonist.28

Genetic syndromes associated with diabetes

A range of genetic syndromes may be associated with insulin resistance and type 1 or type 2 diabetes, including Turner syndrome, Prader-Willi syndrome, Klinefelter syndrome, Down syndrome, and Friedrich’s ataxia.29 These conditions are not discussed further, while some of the rare monogenic disorders associated with complex syndromes are summarized in Table II. The syndromes may either present early as NDM or later in life. Although treatment with dietary modification and oral agents may be used initially, insulin will usually be

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Inheritance</th>
<th>Clinical syndrome</th>
<th>Other clinical features</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary insulin signaling defects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INSR</td>
<td>19p13.2</td>
<td>Recessive or dominant</td>
<td>Severe IR (receptor defect)</td>
<td>Diabetes with very high insulin requirements, leptin decreased, adiponectin normal or elevated</td>
<td>(77)</td>
</tr>
<tr>
<td>AKT2</td>
<td>19q13.2</td>
<td>Dominant</td>
<td>Severe IR (postreceptor defects)</td>
<td>Non obese, hyperinsulinemia</td>
<td>(78)</td>
</tr>
<tr>
<td><strong>Adipose tissue abnormalities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AGPAT2, BSCL2</td>
<td>9q34.3, 9q34.3</td>
<td>Recessive</td>
<td>Berardinelli–Seip syndrome (congenital generalized lipodystrophy)</td>
<td>Diabetes in adolescence, hepatic steatosis, severe dyslipidemia (high triglycerides, low HDL cholesterol), decreased leptin and adiponectin</td>
<td>(79)</td>
</tr>
<tr>
<td>MC4R</td>
<td>18q21.32</td>
<td>Dominant</td>
<td>Monogenic obesity</td>
<td>Tall stature, morbid obesity, increased leptin, diabetes</td>
<td>(80)</td>
</tr>
<tr>
<td>LEP</td>
<td>7q32.1</td>
<td>Recessive</td>
<td>Monogenic obesity</td>
<td>Hypogonadism, morbid obesity, low leptin, diabetes</td>
<td>(81)</td>
</tr>
<tr>
<td>LMNA</td>
<td>1q22</td>
<td>Dominant</td>
<td>Partial lipodystrophy (Familial partial lipodystrophy type 2; FPLD2)</td>
<td>Insulin-resistant diabetes, acanthosis nigricans, hypertriglyceridemia, myopathy and cardiomyopathy</td>
<td>(82)</td>
</tr>
<tr>
<td>PPARG</td>
<td>3p25.2</td>
<td>Dominant</td>
<td>Partial lipodystrophy</td>
<td>Insulin resistant diabetes, hypertension</td>
<td>(83)</td>
</tr>
<tr>
<td>POLD1</td>
<td>19q13.3</td>
<td>Dominant</td>
<td>MDPL syndrome (partial lipodystrophy)</td>
<td>Mandibular hypoplasia, deafness, progeroid features</td>
<td>(84)</td>
</tr>
<tr>
<td>PK3R1</td>
<td>5q13.1</td>
<td>Dominant</td>
<td>SHORT syndrome (partial lipodystrophy)</td>
<td>Short stature, hyperextensible joints, insulin resistance, diabetes</td>
<td>(85)</td>
</tr>
<tr>
<td><strong>Complex syndromes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALMS1</td>
<td>2p13.1</td>
<td>Recessive</td>
<td>Alström Syndrome (ciliopathy-related insulin resistance and diabetes)</td>
<td>Progressive visual impairment (cone-rod dystrophy), sensory neural hearing loss, obesity, acanthosis nigricans, hyperlipidemia, insulin resistant diabetes</td>
<td>(86)</td>
</tr>
<tr>
<td>BB1 to BB18</td>
<td>11q13.2</td>
<td>Recessive</td>
<td>Bardet-Biedl (ciliopathy-related insulin resistance and diabetes)</td>
<td>Intellectual disability, progressive visual impairment (cone-rod dystrophy), polydactyly, obesity, diabetes (50%), renal dysplasia, hepatic fibrosis, hypogonadism</td>
<td>(87)</td>
</tr>
<tr>
<td>WRN</td>
<td>8p12</td>
<td>Recessive</td>
<td>Werner Syndrome (DNA damage repair disorder)</td>
<td>Scleroderma-like skin changes, cataract, subcutaneous calcification, premature atherosclerosis, prematurely aged facies, diabetes</td>
<td>(88)</td>
</tr>
<tr>
<td>BLM</td>
<td>15q26.1</td>
<td>Recessive</td>
<td>Bloom syndrome (DNA damage repair disorder)</td>
<td>Pre- and postnatal growth retardation, sun-sensitive hypo- and hyperpigmented skin, predisposition to malignancy, diabetes</td>
<td>(89)</td>
</tr>
<tr>
<td>PCNT</td>
<td>21q22.3</td>
<td>Recessive</td>
<td>Osteodysplastic primordial dwarfism</td>
<td>Intrauterine growth retardation, severe proportionate short stature, microcephaly, diabetes (~ 50%)</td>
<td>(90)</td>
</tr>
</tbody>
</table>

Table II. Classification of syndromes of severe insulin resistance (IR).

**Abbreviations:** FPLD2, familial partial lipodystrophy type 2; IR, insulin resistance; MDPL syndrome, mandibular hypoplasia, deafness, progeroid features, and lipodystrophy; Ref, reference; SHORT syndrome, short stature, hyperextensibility, herna, ocular depression, Rieger anomaly, and teething delay.

required eventually for the majority of these disorders. While collectively these conditions represent a small proportion of diabetes overall, it is important to consider the possibility of a monogenic disorder when diabetes is associated with multisystem extrapancreatic features.

Mitochondrial diabetes
The most common form of mitochondrial diabetes is caused by the m.3243A>G mutation in mitochondrial DNA. Diabetes onset is usually insidious but approximately 20% of patients have an acute presentation, even in diabetic ketoacidosis. Diabetes typically presents in adulthood, although it may present during childhood and adolescence. Early-onset diabetes is associated with the m.3243A>G mutation, and may be a feature of multiorgan diseases such as Kearns-Sayre syndrome (ophthalmoplegia, degeneration of retinal pigmentation, cardiomyopathy, deafness), MELAS syndrome (myopathy, encephalopathy, lactic acidosis, and stroke), and Pearson marrow-pancreas syndrome. Penetrance is high, with the majority of mutation carriers developing diabetes by age 70 years. Affected females always transmit the mutation, but may be unaffected, while males do not. Initial therapy can be with diet or oral hypoglycemic agents, but insulin is generally required within months or years. Metformin should be avoided as it interferes with mitochondrial function and may trigger episodes of lactic acidosis.

Neonatal diabetes
NDM is a monogenic form of diabetes that presents in the first 6 months, although it may be diagnosed between 6 and 12 months of age in a small number of cases. In contrast, autoimmune type 1 diabetes is extremely rare before age 6 months and when islet autoantibodies are present in this age group, mutations in FOXP3 or STAT3 account for most cases. NDM is rare, with an incidence of 1 in 100 000 to 500 000 live births (Table III). Approximately half of them have permanent diabetes (PNDM), requiring lifelong treatment. The remaining cases have transient neonatal diabetes mellitus (TNDM), with remission of diabetes after weeks or months (although it might relapse later in life). While most cases of NDM

Table III (above and right page). Classification and clinical features of monogenic diabetes with onset in neonates and early childhood.
Abbreviations: CNS, central nervous system; IPEX, immune dysfunction, polyendocrinopathy, enteropathy, X-linked; PNDM, permanent neonatal diabetes mellitus; TNDM, transient neonatal diabetes mellitus; Ref, reference; T1D, type 1 diabetes.
have isolated diabetes, a range of extrapancreatic clinical features may be present (Table III). Many are born small for gestational age, which reflects the negative effects of prenatal insulin deficiency on intrauterine growth. Approximately two thirds of TNDM cases are caused by abnormalities in an imprinted region on chromosome 6q24, while most of the remaining cases are caused by activating mutations in either of the genes encoding the two subunits of the ATP-sensitive potassium (K\textsubscript{ATP}) channel of the \(\beta\)-cell membrane (KCNJ11 or ABCC8). A minority of cases of TNDM is caused by mutations in other genes (Table III). The most common causes of PNDM in nonconsanguineous populations are mutations in the K\textsubscript{ATP} channel or INS gene, with Wolcott-Rallison syndrome or homozygous/compound heterozygous mutations in the GCK gene the most common etiologies in the setting of consanguinity. However, approximately 30% of cases of PDNM do not have a recognized genetic abnormality. If parents are related, Wolcott-Rallison syndrome or homozygous mutations in the GCK gene are the most common etiologies.

**Neonatal diabetes due to mutations in the K\textsubscript{ATP} channel genes**

ATP-sensitive potassium (K\textsubscript{ATP}) channels are cell metabolic sensors that couple cellular metabolic status to electric activity. In pancreatic \(\beta\) cells, the K\textsubscript{ATP} channels are octameric structures composed of four Kir6.2 subunits—encoded by the KCNJ11 gene—that form the channel pore, surrounded by four sulfonylurea receptors (SURs) encoded by the ABCC8 gene. They play an important role in glucose homeostasis, by modulating insulin secretion in response to fluctuations in plasma glucose levels. An increase in metabolic activity within the \(\beta\) cell increases the ATP/ADP ratio; this closes the K\textsubscript{ATP} channels, leading to cell membrane depolarization, an influx of intracellular calcium and consequent insulin secretion. Activating mutations in KCNJ11 or ABCC8, which prevent K\textsubscript{ATP} channel closure and therefore insulin secretion in response to glucose, are the most common cause of PNDM and the second most common cause of TNDM (Table III). Mutations in KCNJ11 are more commonly associated with PNDM versus TNDM (90% versus 10%), while mutations in ABCC8 more

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Inheritance</th>
<th>Diabetes</th>
<th>Other clinical features*</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCNJ11</td>
<td>11p15.1</td>
<td>Spontaneous or dominant</td>
<td>PNDM/ TNDM</td>
<td>Most common cause of PNDM (90%); may be associated with developmental delay, with or without epilepsy; most respond to sulphonylurea therapy</td>
<td>(66)</td>
</tr>
<tr>
<td>ABCC8</td>
<td>11p15.1</td>
<td>Spontaneous, dominant or recessive</td>
<td>TNDM/ PNDM</td>
<td>Most common cause of TNDM (66%), may be associated with developmental delay with or without epilepsy; most respond to sulphonylurea therapy</td>
<td>(67)</td>
</tr>
<tr>
<td>INS</td>
<td>11p15.5</td>
<td>Recessive</td>
<td>TNDM/ PNDM</td>
<td>Second most common cause of PNDM: may also present as not antibody negative insulin requiring diabetes at a later age; responsive to sulphonylurea therapy</td>
<td>(68)</td>
</tr>
<tr>
<td>GCK</td>
<td>7p15-p13</td>
<td>Recessive</td>
<td>PNDM</td>
<td>Severe intrauterine growth retardation</td>
<td>(69)</td>
</tr>
<tr>
<td>SLC2A2 (GLUT2)</td>
<td>3q26.1-q26.3</td>
<td>Recessive</td>
<td>PNDM</td>
<td>Fanconi-Bickel syndrome (hypergalactosemia, liver dysfunction)</td>
<td>(70)</td>
</tr>
<tr>
<td>SLC19A2</td>
<td>1q23.3</td>
<td>Recessive</td>
<td>PNDM</td>
<td>Roger's syndrome: (thiamine-responsive megaloblastic anemia, sensorineural deafness)</td>
<td>(71)</td>
</tr>
<tr>
<td>INS</td>
<td>11p15.5</td>
<td>Spontaneous or dominant</td>
<td>PNDM</td>
<td>Isolated PNDM</td>
<td>(72)</td>
</tr>
<tr>
<td>EIF2AK3</td>
<td>2p11.2</td>
<td>Recessive</td>
<td>PNDM</td>
<td>Wolcott-Rallison syndrome: spondyloepiphyseal dysplasia, recurrent hepatic and/or renal dysfunction, diabetes may not present until age 3-4 years</td>
<td>(73)</td>
</tr>
<tr>
<td>IER3IP1</td>
<td>18q21.2</td>
<td>Recessive</td>
<td>PNDM</td>
<td>Microcephaly, lissencephaly, epileptic encephalopathy</td>
<td>(74)</td>
</tr>
<tr>
<td>FOXP3</td>
<td>Xp11.23-p13.3</td>
<td>X-linked, recessive</td>
<td>T1D</td>
<td>IPEX syndrome: autoimmune enteropathy, eczema, autoimmune hypothyroidism, elevated IgE</td>
<td>(32)</td>
</tr>
<tr>
<td>WFS1</td>
<td>4p16.1</td>
<td>Recessive</td>
<td>Insulin requiring diabetes**</td>
<td>Wolfram Syndrome: progressive optic atrophy (typically after diabetes onset), central diabetes insipidus, sensorineural deafness, mental retardation, seizures</td>
<td>(75)</td>
</tr>
<tr>
<td>CFTR</td>
<td>7q31.2</td>
<td>Recessive</td>
<td>Insulin requiring diabetes***</td>
<td>Cystic fibrosis: progressive deterioration in glucose tolerance; diabetes in ~ 35%</td>
<td>(76)</td>
</tr>
</tbody>
</table>

*Characteristics are variably present / **Mean age of diagnosis ~ 5 years / ***Age of diabetes diagnosis ~ 18-24 years
frequently cause TNDM (approximately 66%). Approximately 20% of patients with mutations in KCNJ11 may have associated neurological features, in keeping with the expression of KATP channels in neurons and muscle cells, while neurological abnormalities are less common and milder in those harboring ABCC8 mutations. The most severe neurological phenotype is known as DEND (developmental delay, epilepsy and neonatal diabetes) syndrome, with an intermediate form of DEND syndrome (iDEND) that is characterized by milder motor speech or cognitive delay and patients typically do not have epilepsy. There is also some evidence that all patients with KATP channel mutations have defects in developmental coordination (particularly visual-spatial dyspraxia) or attention deficits.30

◆ Neonatal diabetes due to INS mutations
Heterozygous coding mutations in the preproinsulin gene (INS) are the second most common cause of PNDM after KATP channel mutations. The mutation usually results in a misfolded proinsulin molecule that is trapped and accumulates in the endoplasmic reticulum, leading to endoplasmic reticulum stress and β-cell apoptosis.37 Similar to infants with KATP channel mutations, intrauterine growth retardation is typical; however, diabetes presents at a slightly later age in those with INS mutations and they do not develop neurological features as a direct consequence of the mutation.

◆ Neonatal diabetes due to GCK mutations
Mutations in GCK are responsible for approximately 2% to 3% of cases of PNDM overall.31 In contrast to the asymptomatic phenotype of CGK-MODY due to heterozygous GCK mutations, homozygous or compound heterozygous mutations prevent the β cells from secreting insulin in response to hyperglycemia. The diagnosis should be considered in neonates who develop diabetes within the first few days of life whose parents have asymptomatic mild hyperglycemia (and harbor heterozygous mutations in GCK). Unlike KCNJ11 and ABCC8 mutations, patients are not responsive to sulfonylurea therapy and lifelong insulin treatment is required.

◆ Other causes of neonatal diabetes
The clinical characteristics of other causes of neonatal and infancy-onset diabetes are shown in Table III. Apart from KATP channel NDM, all other causes need to be treated with subcutaneous insulin. Patients with pancreatic aplasia/hypoplasia also require exocrine pancreatic supplements.

◆ Treatment of neonatal diabetes
Initial treatment of NDM involves metabolic stabilization (since many cases present with severe dehydration, failure to thrive, and diabetic ketoacidosis). Insulin therapy should be commenced initially and a sample sent for molecular genetic diagnosis as soon as possible. Many laboratories will provide a rapid result (within 1 to 2 weeks) as to whether the infant has a mutation in KCNJ11 or ABCC8, in which case high-dose sulfonylurea therapy should be initiated. The majority (90%) of patients with KATP channel mutations can be transferred from insulin to sulfonylurea therapy. The doses required are high (based on mg/kg body weight) compared with adults with type 2 diabetes. The typical dose is 0.5-1.0 mg/kg/day of glibenclamide, although higher doses may be required. The main side effects are hypoglycemia, transient diarrhea, and staining of the teeth. Sulfonylurea drugs may penetrate the blood-brain barrier and there is some evidence that sulfonylurea therapy may partially improve the associated neurological symptoms36; for this reason the higher range of the dose scale is recommended for patients with DEND or iDEND syndrome. For TNDM a much lower starting dose of glibenclamide is recommended (0.05 mg/kg/day); tapering upward or downward is often needed and eventually therapy will be ceased as the TDNM resolves. Patients with NDM due to INS mutations do not respond to sulfonylurea therapy and therefore insulin therapy is required.

Monogenic insulin resistance syndromes
Rare monogenic forms of severe IR can also cause diabetes, although diabetes is less common than in monogenic disorders leading to β-cell failure, particular before the onset of puberty. Classified according to their pathophysiology, there are three broad groups of IR: primary insulin signaling defects, IR secondary to adipose tissue abnormalities, and IR as a feature of complex syndromes, including ciliopathy-related diabetes.39 The genetic, clinical, and biochemical features of disorders within these three groups are shown in Table II.

Characteristics of IR syndromes include moderate to severe acanthosis nigricans associated with markedly elevated serum insulin concentrations or high insulin requirements in those with diabetes, in the absence of significant obesity. Female patients often present during adolescence with ovarian hyperandrogenism, resulting in a gender bias in the diagnosis. Variable other clinical features may help to guide specific genetic testing (see Table II).

The mainstay of therapy for lipodystrophies includes dietary advice with a low-fat, sometimes hypocaloric diet, with the aim of ameliorating metabolic derangements. In partial lipodystrophy, insulin sensitizers such as metformin and glitazones may be effective. Recombinant leptin has been used to treat patients with severe congenital lipodystrophy.40

Investigation of monogenic diabetes – rationale
Molecular genetic testing is both sensitive and specific for diagnosing monogenic diabetes, and is now available in many countries globally, with many laboratories offering rapid turnaround times, particularly for NDM. Molecular genetic testing is recommended at the time of diagnosis of NDM, since this will enable definition of the subtype, which impacts on treatment decisions such as use of sulfonylureas. Genetic testing should be strongly considered in patients who are suspected to have other forms of monogenic diabetes. A family
history of diabetes is not essential to prompt genetic testing, as de novo mutations may occur. For example, spontaneous mutations and deletions are found in up to two-thirds of cases of MODY due to HNF1B,30 90% of heterozygous activating mutations in KCNJ11 that cause NDM arise de novo, and the majority of heterozygous INS mutations are sporadic de novo mutations, with a family history of autosomal dominant NDM present in only approximately 20% of cases. Informed consent should be obtained prior to testing from the individuals tested and their legal guardian as appropriate. Referral to a specialist team (diabetes genetics or clinical genetics) is recommended, particularly when testing of asymptomatic individuals is requested.

Conclusions
Advances in molecular genetics have contributed to unravelling the heterogeneity of diabetes and identification of clinically distinct subgroups. Although our current understanding is that monogenic diabetes contributes to no more than 5% of diabetes cases overall, the clinical implications of the diagnosis for the individual and their family support the use of genetic testing in specific cases. In particular, the absence of classical features of type 1 or type 2 diabetes, early onset of disease before the age of 6 months, and presence of extrapancreatic features warrant consideration of a genetic form of diabetes. Careful characterization of the phenotype is important to guide testing of specific genes.

References

Monogenic diabetes: advances in diagnosis and treatment – Craig

MEDICOGRAPHIA, Vol 38, No. 1, 2016

UP TO 15

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Stofflers DA, Zinkin NT, Stanioyevich V, Clarke WL, Habener JF. Pancreatic age-

Keywords: c-peptide; familial; glucokinase; hepatic nuclear factor; insulin; MODY; monogenic diabetes; neonatal diabetes; sulfonylurea

AVANCÉES DIAGNOSTIQUES ET THÉRAPEUTIQUES DANS LE DIABÈTE MONOGÉNIQUE

Le diabète monogénique représente environ 1 à 5 % des cas de diabète chez les jeunes. Ces dernières années, son incidence a augmenté parallèlement à une plus grande sensibilisation et une meilleure disponibilité des tests génétiques. Le diabète monogénique résulte de la présence d’une ou plusieurs anomalies dans un seul gène et plus de 20 gènes différents ont été impliqués dans son développement. Les deux principaux sous-types sont le diabète néonatal et le diabète de type adulte chez le jeune (MODY). Les mutations du gène du facteur nucléaire 1a hépatocytaire HNF1A (hepatocyte nuclear factor 1a) sont la cause la plus fréquente de diabète familial autosomique dominant tandis que les mutations du gène de la gluco-kinase (GCK) sont la cause la plus courante d’hyperglycémie persistante, légère et asymptomatique dans la population pédiatrique. Le diabète néonatal, qui se manifeste typiquement avant l’âge de 6 mois, est souvent dû à une mutation dans un des trois gènes suivants : KCNJ11, ABCC8 ou INS. Le diagnostic de diabète monogénique peut être suspecté en présence d’une ou plus des caractéristiques suivantes : (i) diabète présent avant l’âge de 6 mois ; (ii) antécédents familiaux importants de diabète ; (iii) absence d’auto-anticorps anti-ilots de Langerhans ; (iv) besoins faibles ou nuls en insuline 5 ans après le diagnostic ; (v) absence de caractéristiques cliniques d’un diabète de type 2 ; (vi) hyperglycémie à jeun modérée et stable ; (vii) diabète associé à des atteintes extra-pancréatiques. Le diagnostic de diabète monogénique peut significativement influer sur la prise en charge du patient en permettant de prédire l’évolution de la maladie et de mettre en place un traitement approprié. Certaines formes de MODY sont sensibles aux sulfonylurées mais l’hyperglycémie à jeun modérée due aux mutations de la GCK n’est pas évolutif et ne nécessite aucun traitement.
A TOUCH OF FRANCE

In Japan, many women cover their mouths out of modesty when they smile or laugh, while in other countries merriment is concealed out of fear of the evil eye. For most of us, an open smile is a natural thing; yet smiling in public is a recently acquired habit. Only a couple of centuries ago, the dental state of most people was so appalling that aristocrats and bourgeois took great care to avoid being seen baring their teeth, leaving expressions of joy and mirth to the commoners. Read the story about the man who first liberated the smile, and the woman who first captured it on canvas. The time? The 18th century. The place? Where else but in France! Today’s Touch of France section should bring the touch of a smile to your face!

The rise and fall of the smile in 18th-century Paris
A study in dentistry

C. Jones, UK
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Élisabeth Vigée Le Brun, painter of the smile

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The iconic self-portrait of Élisabeth Louise Vigée Le Brun with her daughter: Maternal Tenderness. (1786). Oil on oak panel, 106x84 cm). Photo © RMN - Grand Palais (Musée du Louvre)/ Frank Raux.
In eighteenth-century Europe, tooth loss after a certain age was the norm. It usually began before one’s forties and proceeded at a steady, unrelenting pace. With teeth vanished good looks. Capacity for speech suffered too, and talking transmuted into an affair of grunts and whistles. Discomfort, inconvenience, problems with chewing food, chronic indigestion, halitosis, and facial disfigurement caused by the bad state of the mouth were the substance of everyday middle-aged life.

The rise and fall of the smile in 18th-century Paris
A study in dentistry

by C. Jones, United Kingdom

Colin Jones, CBE, is Professor of History at Queen Mary University of London. In 2015, he was Carl and Lila Pforzheimer Fellow at the National Humanities Center in North Carolina. He is a Fellow of the British Academy and immediate Past President of the Royal Historical Society. He is the author of many books and articles on the history of France, and specializes in the French Revolution, the history of medicine, and the history of Paris. His books include The Great Nation: France From Louis XV to Napoleon, 1715-1799 (Penguin, 2002); Paris: Biography of a City (Penguin, 2004), winner of the Enid MacLeod Prize of the Franco-British Society; and, most recently, The Smile Revolution in 18th-Century Paris (Oxford University Press, 2014).

Madame Vigée Le Brun’s 1787 self-portrait, depicting her smiling and showing white teeth, seems a very modern form of self-representation. Yet when it was displayed at the Paris Salon, it attracted hostility as an unwelcome and unseemly innovation. The present article suggests that this smile can be tracked back partly through changes within French culture (including painting) in the eighteenth century, and partly through the emergence of dentistry. The age witnessed the passage from tooth-pulling to preventive dentistry, a movement led by Pierre Fauchard, the “Father of Modern Dentistry.” The demand for the kind of smile that Fauchard and his Parisian disciples could produce linked to wider changes within French culture: a move away from the formal style of bodily comportment associated with the royal court; a greater openness toward the display of the emotions; and a belief, that claimed to be grounded in science, that a smile of sensibility was a truthful representation of an individual’s inner essence. Yet though the smile of sensibility appeared to be carrying all before it by the late 1780s, the 1789 Revolution saw its calamitous decline. Again this linked to cultural and political changes, but also to the decline of French dentistry. The white-tooth smile would only reappear as a badge of individual identity in the twentieth century—and initially in the USA rather than in France. The cultural models offered by celebrity stardom and commercial advertising counted for something in this. So did the advent of excellent dentistry.

Medicographia. 2016;38:110-121 (see French abstract on page 121)
In the autumn of 1787, the painter Madame Élisabeth Louise Vigée Le Brun displayed a self-portrait at the Paris Salon, the celebrated biennial art exhibition held in the Louvre (which still houses the painting). She portrayed herself dandling her daughter on her lap, and with her own mouth set into a pleasing smile, her lips parting to reveal white teeth.

In our own day, a white-tooth smile like this is a banal and unremarkable social gesture. Projected by politicians, film stars, and advertising models, and adorning our own faces as soon as a camera hoves into view, it stares out at us from screens, billboards, and a million photo albums. Yet the 1787 Vigée Le Brun smile provoked a scandal. “An affectation which artists, connoisseurs, and people of good taste are unanimous in condemning,” noted a journalist, “and of which no example is found in Antiquity, is that in smiling Madame Vigée Le Brun shows her teeth.” Her evidently surprising smile seemed in its way quite as revolutionary as the political events which soon, in 1789, became the first modern-day Revolution.

Where did this putatively revolutionary smile come from? Why did it excite such harsh criticism? And where, moreover, did it go? For the white-tooth smile is not much in evidence throughout the nineteenth century in painting as in public life. The answer to these questions has much in fact to do with dentistry.

At this very moment in 1787 that saw the sudden and shocking blossoming of the white-tooth smile, the quality of mouth care offered in the French capital was in fact unrivalled throughout Europe and the wider world. Symptomatically, it was the French who gave the world the very word “dentist.” It arrived in English in the 1750s, but was a direct translation of the French word dentiste. That term had entered the French language in 1728, coined by the French practitioner Pierre Fauchard in his erudite two-volumed work Le Chirurgien Dentiste, ou Traité des Dents [The Dentist Surgeon, or Treatise on the Teeth]. Fauchard offers a rare—possibly unique—example of a dentist famous enough to be commemorated on a postage stamp, while the Pierre Fauchard Academy, the prestigious honorary organization for dentists worldwide, honors him as the “Father of Modern Dentistry.” So crucial was Fauchard in changing the quality of mouth care in the eighteenth-century French capital that it is indeed tempting to see Madame Vigée Le Brun’s smile as in some senses an advertisement for Parisian dentistry.

The old régime of teeth
To grasp the extent of Fauchard’s influence and the impact of his example, we have only to explore the way that teeth were cared for before his arrival on the Parisian scene. In the Old Regime of Teeth, which characterized all of early modern Europe prior to this period, care of teeth was low on individuals’ agendas. Tooth loss after a certain age was the norm. It usually began before one’s forties and proceeded at a steady, unrelenting pace. With teeth vanished good looks. Capacity for speech suffered too, and talking transmuted into an affair of grunts and whistles. Discomfort, inconvenience, problems with chewing food, chronic indigestion, halitosis, and facial disfigurement caused by the bad state of the mouth were the substance of everyday middle-aged life.

It was thus little wonder that people shunned smiling with an open mouth: the look might be too ghastly for tranquil contemplation. The problem did not seem to be getting any better, moreover: the arrival of colonial sugar in the diets of the urban middling and laboring classes probably made the state of their teeth worse in the eighteenth century than in any prior period of European history.

The Old Régime of Teeth encouraged utter fatalism about one’s teeth. If one’s teeth did not fall out of their own accord, then the only practitioners engaged in mouth care were specialists in tooth-pulling rather than in any other form of care. At the outset of the eighteenth century, physicians and elite surgeons were massively disinclined to soil their hands with such menial work. It therefore devolved on a group of self-
trained and unqualified individuals whose most striking characteristics were a powerful right arm and a strong wrist. These figures often called themselves “operators on the teeth.” Most contemporaries, however, thought of them as tooth-pullers—and charlatans to boot, for most of them combined tooth-pulling arts with outrageous claims for other medical services, and with various forms of showmanship. From the late sixteenth century, troupes of travelling Italian players had brought the commedia dell’arte repertoire into provincial France, setting up their trestle stages in fairs and market squares for their performances—and doing tooth-pulling on the side. Public tooth-pulling came to be associated with theater, acrobatics, singing, tightrope walking, the display of exotic animals, and comedy routines, plus the retailing of allegedly miraculous snakebite remedies. Tooth-pulling was a performance in itself in fact. One famous tooth-puller, for example, was known for his trick of extracting a tooth with one hand while firing a pistol in the air with the other, and with his head in a sack. Others performed the act of extraction while seated on a horse: from the saddle, they placed the tip of a sword blade on the base of the throbbing tooth, achieving the desired result with a mere flick of the wrist.

The direness of the situation for the care of teeth was well exemplified in the ghastly dental trials of the mighty Louis XIV, king of France from 1643 to 1715. By the late 1670s, when the king was around 40, contemporaries were remarking on the loss of nearly all the king’s teeth. His few remaining teeth required increasing intervention. In his palace at Versailles, Louis had a medical household of dozens of eminent practitioners, but when in 1685 the remaining teeth on the upper right side of his jaw were causing discomfort, he had recourse to a simple tooth-puller operator. Unfortunately, while extracting the teeth, the operator also accidentally took out much of the king’s jaw as well. The perforation of the king’s palate left a gaping hole in his oral cavity. Consequently, when he drank or gargled, the liquid came out through his nose like a gushing fountain. Worryingly, moreover, the hole in the king’s palate became nauseously infected. Realizing that there was simply no other way, Louis’s Premier Surgeon determined to undertake a full-blown operation on the royal mouth. In two fearful sessions, he cauterized the king’s palate, sealing it off from the maxillary sinus. The red-hot iron which the surgeon deployed managed to block up the hole. After an extensive period of healing, the fountain dried up: Louis could eat normally again.

The example highlights the fact that even the most powerful ruler in Europe with the best level of health care that any individual could possibly have had at this time, was as medically unprotected against tooth loss and most mouth ailments as the poorest of his subjects. As he was undergoing the exquisitely painful and utterly exceptional cauterization, Louis is said to have remarked to the surgeons: “treat me like a peasant.” In the Old Régime of Teeth there was no royal road to good mouth care.

The birth of modern dentistry
In stark contrast to this sorry picture, Pierre Fauchard opened a window into a very different world of mouth care: a world in which the aim of professional care was not the removal of teeth, but their preservation as healthy and beautiful adornments to the smiling face. To a considerable extent, Fauchard set the template for what we expect from our dentists in the twenty first century.
Fauchard (1678-1761) initially worked as an itinerant tooth puller, but seems to have been eager to learn about the teeth as an object of scientific knowledge. Based in Paris from the 1710s, he sought out contact with the city’s eminent surgeons. His 1728 Le Chirurgien-Dentiste presented as a noble branch of contemporary Enlightenment science that in the past had been viewed as an ignoble and rough-and-ready art, full of trade secrets. Fauchard’s opus magnum is incomparably longer, more detailed, and more sophisticated about the structure of the mouth and the illnesses of the teeth than any earlier work in any language. Its many illustrations highlighted a new zeal for scientific transparency and for the diffusion of dental knowledge. Fauchard prided himself on publishing freely and openly in the public sphere. This new spirit of scientific openness helped spawn a solid cohort of disciples drawing inspiration from Fauchard’s example. There were soon over thirty of them practicing in Paris. They all adopted the fashionable new title of dentiste.

Dentistry, for Fauchard and his disciples, was less about pulling out painful and diseased teeth, than preventing tooth decay in the first place. In the cause of prevention, they stressed the importance of hygiene in mouth care. Transforming the technical instruments that dental surgeons used allowed them to extend their range of services. They could extract teeth when this was absolutely essential of course, but they also knew how to clean dirty teeth, preventing them going bad, fill cavities, and file uneven teeth; they knew all about the separation and reduction of teeth, cauterizing, straightening, and positioning, “firming” and “trepanning” (drilling to release infected matter). They practiced the transplantation of teeth (an art that was satirized by the English caricaturist Thomas Rowlandson). They whitened as well as cleaning teeth and cared for the gums and the soft parts of the mouth. Some specialized in the creation of dental pieces. Indeed, Fauchard invented the first spring-loaded dentures (which did however, have an unfortunate habit of unexpectedly launching themselves projectively from a client’s mouth at unguarded moments!)

Some folkloric charlatanesque figures continued to prosper in eighteenth-century Paris. The legendary Le Grand Thomas, for example, practiced public tooth pulling on the Pont Neuf every day from the 1710s to the 1750s. However, increasingly, public favor fell on dentists rather than tooth pullers. Moreover, although they claimed scientific status, in fact the new Fauchardian dentists was also highly entrepreneurial. They advertised their wares in newspapers and their publications had a strong commercial as well as a scientific air about them. They stressed how good clean teeth were a necessary accoutrement for those spending their lives in the ambiance of the dynamic Parisian public sphere, urging the virtues of daily self-care by their clients. The invention of the humble toothbrush and its
swift passage into the material paraphernalia of everyday life was a symptom of this change. An early example—namely, Napoleon Bonaparte’s monogrammed implement—may be viewed in the Wellcome Collection in London. And in 1788—around the same time that Madame Vigée Le Brun’s portrait smiled out so brazenly in the Salon—the Parisian surgeon Nicolas Dubois de Chémant launched porcelain white dentures, the very first of their kind. Far superior to their predecessors, they allowed the new white-tooth smile to be displayed even by individuals without a tooth of their own in their heads. By the 1780s, Parisian dentistry was thus on top of the world. Practitioners from other countries could only look enviously or emulatively on. In no other city in the world was the dentist such an established feature of the urban landscape. Nowhere else could such a figure boast a more willing, devoted and well-heeled clientele. Fauchard’s disciples acquired international fame. Before she sent her daughter, Marie-Antoinette, to France in 1770 to marry the future Louis XVI, the Austrian Empress Maria Theresa thought it wise to summon to Vienna the very best that Europe could provide to repose some of the princess’ teeth so that they would look “very beautiful and well arranged.” Her choice fell on a Parisian dentist. Across the Atlantic, when in the early 1780s the future first President of the United States, George Washington, was having toothache troubles, he availed himself of the expertise of a French expatriate dentist. Grand Tourists now made their stay-over in Paris the time for a dental checkup. Even the Italian roué Casanova, his charms failing and his teeth falling out, turned in desperation to Parisian dentures on the eve of the Revolution. The Parisian dentist really had arrived.
Smiles of sensibility

Historians of science and technology sometimes argue that inventions and innovative breakthroughs create their own market. In fact, it is rarely quite as simple. Although it is true that the entrepreneurial skills displayed by Parisian dentists helped stimulate demand for a white-tooth smile, that demand preexisted them. In the decades immediately following the death of Louis XV, even before Fauchard’s influence had started to make itself felt, a new kind of smile was starting to evolve that highlighted more natural modes of facial expression and good, healthy white teeth. This was the smile of sensibility.

The smile of sensibility evolved over the course of the eighteenth century as a reaction against the kind of smiling and facial comportment to be found at the royal court. Smiling was the exception at Versailles. The strictly-maintained preference there was for grave, mobile physiognomies that exuded dignitas and gravitas. Hyacinthe Rigaud’s 1701 portrait of Louis XIV captures the mood exactly. Yet if the painting is all the more intriguing in that the ruler’s hollow cheeks reveal his toothlessness, the main reason disposing the king to keep his mouth shut was starting to evolve that highlighted more natural modes of facial expression and good, healthy white teeth. This was the smile of sensibility.

Cultural disapproval of open lips was based on the feeling that the gaping and toothless or gap-filled mouth was ugly and indecorous and indeed often quite disgusting. Opening the mouth was simply not good form—any more than picking the nose, eye-rubbing and squinting, cleaning out the ears, scratching the arse and, especially, unrestrained farting. Keeping the mouth shut was an important element within a more general and systematic policing of bodily orifices. The open mouth was like a Pandora’s box. If one smiled or laughed, then, it should be with mouth shut. No wonder Mona Lisa had not shown her teeth!

Louis XIV’s penchant for melancholic facial impassivity set the tone at court and provided the rules that courtiers lived by. Courtiers emulated their ruler in everything, but also eschewed expression of emotion because they were afraid of giving away their innermost feelings in the competitive aura of the royal court. The white face-paint they wore, known as le fard, made them seem like identikit marble statues. Overwhelmingly, the smiles that emanated from the court were sardonic, ironic, disdainful, proud, knowing, and contemptuous. A smile denoted not human camaraderie or spontaneous gaiety of heart, but elevated social distance, de haut en bas. One smiled snootily down, as indeed one laughed down, at the misfortunes of others. A gentleman’s smile was thus an unconvincing and artificial gesture that marked distinction and reinforced social hierarchy.

Where then did the Vigée Le Brun smile come from? A less stiff and overly dignified demeanor seems to have become more popular almost as soon as Louis XIV was dead. With
his successor Louis XV merely a child, the Regent, the duc d’Orléans, abandoned Versailles for the pleasures of the capital and encouraged a much more open and freewheeling atmosphere among the social and political elite—that was, however, set back by Louis XV’s assumption of sole power in 1723. The young king returned the court to Versailles and for the remainder of his very long reign (he only died in 1774) punctiliously reimposed his predecessor’s formal and majestic protocol.

Yet while the court at Versailles seemed locked in the timeless rules of dignitas and gravitas, Paris was on the move. This showed initially in the more natural and accepting way that theater, fiction, and then art represented the human emotions and their free expression. From the 1720s and 1730s, so-called comédies larmoyantes, literally “tearful comedies,” became highly fashionable. Their plots featured everyday misfortunes that befall virtuous individuals, but which are resolved happily, with tears and smiles all round. Fiction took up the baton. The great novels of sensibility of the age—English author Samuel Richardson’s Pamela, Clarissa, and The History of Sir Charles Grandison, which were translated into French in the 1740s and 1750s, and especially Jean-Jacques Rousseau’s Julie, ou La Nouvelle Héloïse, published in 1761—gave the new smile cultural traction, causing a breakthrough in usage in French literary culture. The incidence of smiling in novels increased sharply and enduringly. And although the old malign courtier smile was still in place, it was now swamped by “natural” smiles said to be “enchanting,” “sweet,” “good,” “agreeable,” “friendly,” and “virtuous.” Such smiles were no longer exchanged de haut en bas, but rather between moral equals. And increasingly they revealed white teeth.

Although portrait painting was initially slow to react—as the furore caused by Madame Vigée Le Brun in 1787 showed—genre painting started reflecting and relaying the smiling trend, particularly after 1750. Jean-Baptiste Greuze in particular could almost be accounted as an illustrator of the novels of sensibility, tears, smiles and all. Importantly, too the science of physiologists such as Thomas Willis and Albrecht von Haller gave sensibility endorsement as a core feature of the human makeup. Men and women, they argued, were made to be moved emotionally, and tears and smiles were thus the everyday currency of normal human exchange. The smile was thus no longer a hierarchical gesture of disdain or condescension, but an egalitarian sharing of self. It was also a token of a new and more optimistic account of human character. This chimed with the philosophy of perfectibility abroad in Enlightenment circles. The smile triggered optimism about the present and the future. It also fitted rather well within the institutions of sociability in Enlightenment Paris. Salons, promenades, coffee-houses and the like provided a more egalitarian and more accommodating framework for face-to-face encounters in which a smiling demeanor prevailed. Courtiers at Versailles still emulated the facial impassivity of their royal master. But citizens in the Parisian public sphere took their cues from the demeanor of the heroes of their favorite plays, paintings and, especially, novels. Crying, laughing, and smiling now became acceptable public gestures among the Parisian elite and middling classes, who seemed to be weaning themselves off cultural dependence on the model of behavior performed at Versailles. And thanks to Fauchard and his ilk, smiles on the stage, on the page, in the frame, and in everyday life, smiles now had pure white teeth.
The decline of the smile of sensibility

Had Helen of Troy lost a front tooth, Louis-Sébastien Mercier noted in 1788, the Trojan War might never have taken place. This philosophical quip about the role of accidents in history highlights how much of human beauty and individual identity in late-eighteenth-century Paris was thought to be invested in the smile, particularly the open-mouth, white-tooth smile of sensibility.

Yet in the event Madame Vigée Le Brun and, to a lesser extent, dentures-manufacturer Dubois de Chémant were not to be harbingers of a new dawn of human sensibility. The French Revolution of 1789 caused the white-tooth smile to go into abeyance for most of the ensuing century. The reasons for this are many and varied. But like the rise of the white-tooth smile its decline was a complicated process that interwove technical changes and cultural shifts.

Partly at least, the decline of the Parisian smile was a matter of dentistry. The science and professional practice of dentistry went into headlong retreat from the 1790s and the early nineteenth century witness saw their calamitous collapse. The productive niche that dentists had occupied within the pre-Revolutionary medical system was ended by Revolutionary legislation, and no proper training was established for a career in dental surgery. With no institutional status, dentists soon found themselves competing again with the tooth-pulling charlatans of old. It was not until the very end of the nineteenth century that French dentistry began to professionalize—or rather reprofessionalize. This made the country a laggard behind its international rivals, notably the USA, where professionalization had begun in the 1830s and 1840s. In France, the erstwhile leader of world dentistry, the Old Régime of Teeth was back with a vengeance.

The decline of the smile owed much to cultural and political changes too. The mood of the Revolutionary decade—especially as the French nation lurched towards war and Terror (1792-1794)—was generally far too serious for a smile (and all the more for a smile of sensibility) to seem apposite. If there was still plenty of laughter this tended to be either the aristocratic mocking, de haut en bas humor of the counterrevolutionary press or at the other extreme the full-throated plebeian humor generated by the radical popular movement in Paris. In the political mainstream, smiling could now be seen an unpatriotic as well as un-Revolutionary. People kept their heads and their smiles beneath the parapet and out of public view. French Revolutionary political culture fell out of love with the smile. Smiling lost its status as an emergent cultural norm and its iconic status in public life. The Napoleonic era (1799-1815) confirmed the trend, showing marked preference for neoclassical dramatic firmness of facial feature. Napoleon and his nineteenth-century successors would have felt more comfortable with Louis XIV’s facial immobility than with the world that Madame Vigée Le Brun had seemed to be inaugurating.

At a more subliminal level, too, other forces were at work to erode the positive aura around the French smile of sensibility. Prior to 1789, cultivated French men and women associated the open mouth with the new white-tooth smile. From 1789, the open mouth that people associated with the French revolutionaries brought up all manner of disturbing images: the image of the Revolution devouring the revolutionaries as Saturn devoured his children; the quasi-cannibalistic zest of the sansculotte buveur de sang; the facial mutilations of victims of crowd violence; and the last moments of Maximilien Robespierre, executed with half his jaw hanging off after a botched suicide attempt, uttering a piercing scream as his head met the blade and his remaining teeth hit the basket.

These were the kinds of images of the open mouth—very much in tune with the emergent modes of the gothic, the ghoulish, and the melodramatic—that lingered in the imagination from the French Revolution onwards and that crowded out memories of more innocent, smiling times. Even Dubois de Chémant’s gift bestowed on humanity of porcelain teeth were now object of the sarcastic mockery of English caricaturists.

The Parisian smile of sensibility of the late eighteenth century was thus to prove almost as evanescent as the smile itself. The white-tooth smile went into hibernation as a public gesture for over a century. It was only really in the twentieth century that it reemerged—and initially in the USA rather than in France—under the influence of a range of factors, including new, highly visual advertising practices, Hollywood media presentation, and the final reemergence of decent, high-class dentistry. The twentieth century would experience a “smile revolution” of its own completely unaware of the eighteenth-century precursor.
GLOIRE ET DÉCLIN DU SOURIRE DANS LE PARIS DU XVIIIÈME SIÈCLE
PETITE HISTOIRE DE L’ART DENTAIRE

L’autoportrait de Madame Vigée Le Brun daté de 1787 où l’artiste affiche un sourire laissant entrevoir une rangée de dents blanches est à première vue une façon tout à fait moderne de se représenter. Et pourtant ce tableau, exposé au Salon de Paris, s’attira l’hostilité en étant perçu comme une innovation malvenue et inconvenante. Il semble que l’on puisse faire remonter la genèse de ce sourire pour une part à une évolution touchant certains aspects culturels de la société française du XVIIIème siècle (dont la peinture) et d’autre part à l’émergence de l’art dentaire. En effet, cette période vit le passage de l’arrachage des dents à un mouvement mené par Pierre Fauchard (1678-1761) prônant une dentisterie préventive, qui lui valut d’être considéré comme le « Père de la Chirurgie dentaire moderne ». La demande pour le type de sourire rendu possible par Pierre Fauchard et ses disciples parisiens était liée à une volonté plus générale de la société française de prendre ses distances avec l’attitude corporelle guindée qui était celle de la Cour. On s’autorisait désormais à montrer ouvertement ses sentiments. La science du moment était également persuadée qu’un sourire désinhibé était le reflet fidèle de l’essence profonde d’un individu. Pourtant, alors que le sourire semblait avoir totalement gagné droit de cité vers la fin des années 80, la Révolution de 1789 lui imposa un coup d’arrêt brutal. En cause les bouleversements politiques et de société, mais également un déclin de la dentisterie française. Le sourire à pleines dents comme manifestation de soi ne referait son apparition qu’au XXème siècle, et cela d’abord aux États-Unis, avant la France, avec la notoriété des stars hollywoodiennes et le développement de la publicité – sans oublier l’avènement d’une excellente dentisterie.
The Artist Painting a Portrait of Queen Marie-Antoinette.
Self-portrait by Élisabeth Louise Vigée Le Brun; 1790; oil on canvas; 100×81 cm. Florence, Galleria degli Uffizi, Corridorio Vasariano.
© Galleria degli Uffizi, Florence, Italy/Bridgeman Images.
Élisabeth Vigée Le Brun, painter of the smile

by M. Raive, France

In 18th-century France, the men and women of good society posed for a portrait with mouths clamped shut, the better to hide their rotten teeth. Only the common people, simpletons, and dolts dared show their ravaged dentition. So smiles never made it onto canvas. Portraitists depicted their sitters as unsmiling, wooden figures, haughty and disdainful, in keeping with the spirit of the age. But the winds of change were blowing. The philosophers of the 18th-century Age of Enlightenment, notably Jean-Jacques Rousseau, urged people to be themselves. Maternal love was openly displayed by aristocrats, members of the French court, and even by Marie-Antoinette, Queen of France and wife of Louis XVI. Mores became freer and corsets and stays a thing of the past. Advances in hygiene and dentistry meant that people no longer shied away from showing their teeth. French artist Élisabeth Louise Vigée Le Brun (1755-1842) took advantage of this newfound freedom and became the first portraitist in the history of art to encourage her sitters to pose naturally, a smile upon their lips. Using a neoclassical style that doubtless flattered her models, Vigée Le Brun in fact freed herself from the staid poses of the recent past and in so doing wrought a pictorial revolution. Hugely successful in the troubled times leading to the French Revolution, she produced some 900 paintings, 600 of which are portraits, including 30 of Queen Marie-Antoinette. Over 150 of her paintings were shown, some for the first time, at the Grand Palais in Paris at the exhibition Élisabeth Louise Vigée Le Brun (23 September 2015-11 January 2016), which will shortly travel to New York (9 February-15 May 2016) and then Ottawa (10 June-12 September 2016).

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As a portraitist in 18th-century France, Élisabeth Louise Vigée Le Brun knew how to get the best out of her sitters, even if it meant smoothing out facial imperfections and—a great novelty in portraiture—urging them to smile. The powerful had long kept their lips sealed in portraits, leaving unseemly, often toothless smiles to the hoi polloi, buffoons, and the slow-witted.

In a century when a natural demeanor ousted affectation, when the philosopher Jean-Jacques Rousseau waxed lyrical on maternal love and exhorted people to be themselves, Vigée Le Brun emphasized sensuality, an unheard of audacity in the highly codified genre of portraiture. She even dared to paint portraits of people smiling, as progress in dentistry and hygiene emboldened sitters to reveal their teeth.
The beginnings of artistry
The daughter of Louis Vigée, a talent portraitist, Élisabeth Louise was born in Paris in April 1755. Cared for by a nanny till the age of five, she was then educated in a convent, where she delighted in drawing her classmates. Delicate health ended Élisabeth Louise’s convent education when she was eleven, and upon return to the family home Louis Vigée recognized his daughter’s talent for art and introduced her to his artist friends: Joseph Vernet, a painter of maritime scenes, and the portraitist and pastelist Jean-Baptiste Greuze. Vernet advised Élisabeth Louise: “My child, don’t follow any school of painting. Study only the works of the great Italian and Flemish masters. Above all learn as much as you can from nature, the first among masters.” Greuze explained the “magic of colors” and transmitted to Élisabeth Louise his taste for chiffon, pale stoles, and white mirror-like silks: “Never thicken your laces and gauzes,” he advised. That she remembered and understood this injunction is clear from the cloud of airy fabrics that cascade down from the straw hat in her 1784 Portrait of Marie Gabrielle de Gramont, Duchess of Caderousse, who, natural and unpowdered, posed without airs or graces. Élisabeth Louise’s elders opened doors to private collections, where she studied the old masters, while at the Louvre and the Musée du Luxembourg she practiced her art by copying works by Rubens, Rembrandt, Van Dyck, and Greuze himself, from whom she learned how to render delicate carnations, transparency, freshness, and the play of light and shade to enhance a complexion.

When just 17, Élisabeth Louise painted portraits of her mother as a sultana, her brother Etienne as a schoolboy, and the jeweler Jacques-François Le Sèvre, her miserly and strict stepfather, whom she loathed and who hogged her earnings, in The Artist’s Stepfather in Nightcap and Dressing Gown. It was just a matter of time before the high society of the Palais Royal quarter in Paris, where Élisabeth Louise lived, discovered her gifts and commissioned portraits. Duchesses, princesses, countesses and counts, courtesans of the boulevard Saint Germain, everyone who was anyone in late 18th-century Paris came to sit for Élisabeth Louise Vigée who, in January 1776, aged 20, became Madame Vigée Le Brun when she married Jean-Baptiste Pierre Le Brun, the foremost art dealer of the time.

The art of portraiture
In her work as a portraitist, Vigée Le Brun used pastels to produce preliminary sketches on which she subsequently based her oil paintings. The great variety of her portraiture bears witness to a mastery of the science of color and to her ability to improvise costumes and poses. In her memoirs, Souvenirs, published towards the end of a long life, Vigée Le Brun divulged her painterly techniques and artifices. In preparation for a sitting, for instance, she readied her palette half an hour beforehand, to avoid wasting the subject’s time, and emptied her mind of worldly affairs. By engaging sitters in conversation, she discovered their attitudes and put them at ease.

Joseph Vernet (1714-1789), painter and mentor of the artist. Élisabeth Louise Vigée Le Brun; 1778; oil on canvas; 92×0.72 cm. Louvre Museum. © RMN-Grand Palais (Musée du Louvre)/Jean-Gilles Benzi.

“Never thicken your laces and gauzes,” was the expert advice Jean-Baptiste Greuze gave Vigée Le Brun. Her see-through ethereal muslins and silk fabrics soon became a distinguishing feature in many of her paintings. Young Woman Holding a Small Spaniel With Garland of Flowers, aka Madame de Porcin. Jean-Baptiste Greuze (1725-1805); 1774; oil on canvas; 72×57 cm. Angers, Musée des Beaux-Arts. © Musée des Beaux-Arts, Angers, France/ Bridgeman Images.
ease. In an interesting aside on flirtatious aspirations, Vigée Le Brun revealed that male sitters sometimes came for the wrong reasons: “Those fond of my face had me paint theirs, in the hope of pleasing me.”

Vigée Le Brun installed her female sitters comfortably, a footstool under their feet, and then stood back to capture the subject’s bearing and appearance. Above all, she advised, light should fall upon the throats of women, to cast warm tones for the shadow of the collarbone and fine and fresh shades for the bosom. No other painter had Vigée Le Brun’s talent for winning the trust of the women, beautiful or plain, who sat for her. In part because she idealized faces and figures, smoothed away imperfections, used flattering dress styles ranging from oriental to pastoral, gave her lady sitters a soulful and noble expression. In Vigée Le Brun’s own words, she “tried as far as was possible to give the women I painted the attitude and expression of their countenance” and “painted them as if daydreaming.” Vigée Le Brun’s female subjects posed unembellished, without stays and corsets, hair down, sometimes even wearing dresses and ribbons lent by the artist. “As I hated the clothes women wore at the time,” Vigée Le Brun wrote, “I made every effort to render them more picturesque. Once I won the trust of my models, I was able to drape them according to my whim, to place light scarves around their bodies and arms.”

Vigée Le Brun’s skills, spirit, and talent for flattering her models made her the darling of the French court, allowing her to move in elevated social circles and to entertain the upper crust. She invited ladies of the court, courtesans, men of letters and the arts, painters, architects, and financiers to her workshop, which doubled as a salon. Her receptions were so popular that it was not unknown for field marshals to have to make do with sitting on the floor. “We had the taste and time for amusement,” she later wrote in Souvenirs.

Before long this carefree world of joie de vivre would be swept away by the French Revolution and many of the charming heads that Vigée Le Brun immortalized on canvas would prove all too mortal as they fell into baskets beneath the “National Razor,” the guillotine.

**At the Royal Court**

Vigée Le Brun was 24 when first asked to paint a portrait of the queen. Marie-Antoinette had complained to her mother, Maria Theresa of the House of Habsburg, that she had been unable to find a portraitist who “captured” her likeness. So why not try Madame Vigée Le Brun? She had a solid reputation, was highly regarded, and had already painted a dozen portraits and replicas for the court.
Peace Bringing Back Abundance. Élisabeth Louise Vigée Le Brun; 1780; oil on canvas; 102.5x132.5 cm. Paris, Musée du Louvre, Département des Peintures.
© RMN-Grand Palais (Musée du Louvre)/Daniel Arnaudet.
This first portrait, entitled *Marie-Antoinette in Court Dress*, shows the queen in a stiff, formal pose, as was the custom, in a white satin dress with large panniers (hoops used to dis-tend a woman’s dress). She is shown holding a pink rose beside a table bearing her crown atop a cushion. On receiving the picture, the queen’s mother, Maria Theresa of Austria, wrote to her daughter: “Your large portrait delights me.” Everyone wanted to be painted by Vigée Le Brun, to the point that she was unable to accept all the commissions that came her way, even though she produced a portrait every 12 days or so. Her hard-working nature is illustrated in *Souvenirs*, where Vigée Le Brun recounts that when pregnant with her daughter she only stopped working, labor pains notwithstanding, when childbirth was imminent.

Vigée Le Brun’s detailed and accurate accounts of her commissions read like a who’s who of late 18th-century France: Marie-Antoinette, Madame du Barry, the official mistress of Louis XV, the Princess Lamballe, the Duchess of Polignac, princes and counts, not to mention the Duchess of Chartres, who had to wait 12 months before she could be fitted into a busy schedule. Vigée Le Brun’s yearly earnings amounted to a tidy sum: between 20 and 30 thousand livres, which in today’s money is approximately 66 to 100 thousand euros or 75 to 114 thousand dollars US.
The Academy
Vigée Le Brun aspired to membership of the Royal Academy of Painting and Sculpture, but its doors were closed to her because she was married to an art dealer. The Academy’s statutes forbade artists from direct or indirect trading in art, and at this time in France a woman’s station was that of her husband. Monsieur Le Brun thus stood in the way of his wife’s advancement, a problem that was overcome by the intervention of Louis XVI, though Vigée Le Brun was unhappy at the idea of owing a fully merited place to royal favor. Later in life she intimated in Souvenirs that she was initially excluded because of the notorious misogyny of the academicians and the antipathy of the Academy’s director. Be that as it may, the king’s will was imposed and Vigée Le Brun was admitted to the Academy at the age of 28 in May 1783 on the basis of “the reputation of her talents.” She submitted to the Academy a number of portraits together with a historical allegory Peace Bringing Back Abundance, as a “reception piece,” which she hoped would lead to admission to the category of history painters. The success of this symbolic painting, in fact made two years before, irked the Academy, which responded by pointedly omitting to mention into which category Vigée Le Brun had been inducted.

The gathering storm
In 1783, Vigée Le Brun painted Marie-Antoinette in a Muslin Dress, which depicts the queen in a simple loose-fitting chemise dress. This was how the queen dressed at the Petit Trianon, her retreat at Versailles, where she escaped the pressures of the court to entertain a select group of intimates. The queen’s dress and manner in the portrait, though, were seen as frivolous, unbecoming of a monarch, and at odds with her duties to the nation. While other European monarchs were represented as models of virtue, maternal sovereigns, exuding authority and gravitas, here the Queen of France was portrayed as a shepherdess. One contemporary noted that while quick to condemn the queen: “Every woman wanted to have the same dishabille, the same bonnet, that they had seen her wear.” And within two years of Marie-Antoinette being painted in one, the chemise dress had become popular.

But more damage was to come. And this time it was far worse. Marie-Antoinette’s reputation suffered a major blow with the so-called Affair of the Diamond Necklace which broke out in 1785. It was intimated that she had been complicit in a swindle designed to defraud the crown jewelers of the cost of a hugely expensive diamond necklace. Marie Antoinette was, in all likelihood, blameless, but the affair triggered a decline in her popularity and thereafter lingered the image of a profligate queen whose vanity took precedence over the welfare of France and her people. Dislike of the queen, known disparagingly as “the Austrian woman” and seen as a spendthrift with an eccentric life-style, was at its peak. This was the backdrop to the opening on 25 August 1787 of the Salon at the Louvre,
where the place of honor was reserved for Marie-Antoinette and her Children, Vigée Le Brun’s attempt to portray the queen in a more human light. Fearful of a poor reception, more for political than artistic reasons, Vigée Le Brun kept the canvas in her workshop, pretexting a need for a few finishing touches. She sent in its place an empty frame. “Voilà le Déficit” quipped some wag, a gibe that spread through the city and reflected the ill will surrounding Marie-Antoinette, who had already been nicknamed “Madame Déficit.” In the end, Vigée Le Brun sent the portrait, but fearing public hostility dared not accompany it. Her worries were unfounded as the painting was well received and Louis XVI said to her: “I know little of painting, but you make me like it.”

In October 1789, following a demonstration in Versailles by the people of Paris, the king and royal family were forced to reside in Paris, making them effectively prisoners. Too close to the monarchy for comfort, Vigée Le Brun risked incurring the same revolutionary wrath. Her success had set tongues wagging—mutterings about how her behavior was not all that it should be, love affairs, hidden payments. She was accused of moral turpitude, of spending extravagantly, even of burning bank notes for heating. Fearing for her life, Vigée Le Brun left France for Italy with her 9-year-old daughter Julie on the night of October 6, 1789, abandoning her husband, fortune, and paintings.

**Exile**

Vigée Le Brun’s exile was to last 13 years, but her reputation as a portraitist went before her and commissions did not lack. In Naples and Vienna she found others who had fled the Revolution, and from 1795 she spent several years in St Petersburg where she continued to paint the members of polite society. One example is her picture of the Countess Golovina depicted in a red shawl and an ochre yellow turban headband tied in cascading brown hair.

On her return to France in 1802, Vigée Le Brun was lauded by the press and by fashionable society at the court of the Bonapartes. Yet she was restless, haunted by memories of happier times and of friends and acquaintances who had come to a bloody end during the Revolution, notably Marie-Antoinette, and in April 1803 Vigée Le Brun left for England, where she spent two years, in London, Brighton, Bath, and
Knole in Dorset, before returning to France. When not traveling around Europe, Vigée Le Brun continued to paint, including portraits of Caroline Murat, Napoleon’s sister, the Duchess of Berry, the Duchess of Guiche, and the famous Italian opera singer Angelica Catalini, as well as Apotheosis of the Queen, her final (lost) portrait of Marie-Antoinette, and Saint Geneviève, the Patron Saint of Paris, whose face she modeled on her daughter Julie, who had died two years earlier in 1819. Vigée Le Brun divided her time between her country house in Louveciennes (10 kilometers west of Paris), where she spent 8 months of the year, and Paris, where she held dinners and receptions, such as a literary evening in the winter of 1831 graced by François-René de Chateaubriand and Honoré de Balzac. For eight years from 1829, Vigée Le Brun busied herself with writing her memoirs. The first volume of Souvenirs was published in August 1835 and volumes II and III followed in 1837, five years before her death in Paris just short of her 87th birthday. On her gravestone in Louveciennes is the inscription: “Here, at last, I rest.”

The last word on Élisabeth Louise Vigée Le Brun should perhaps be left to Xavier Salmon, curator of the eponymous exhibition at the Grand Palais in Paris (23 September 2015-11 January 2016): “With Madame Vigée Le Brun we straddle two centuries. Her last paintings date from the 1830s, when she is painting as she did in 1780. There is a gulf between her and the romantic painters. She was the artist of joie de vivre in troubled times.”

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