Type 2 diabetes: evidence beyond perception

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There is a widespread perception that we have knowledge in medicine, and that therefore ‘things can be fixed.’ If we know the genome, then we have the handbook of the human machine. Good doctors should therefore be able to make a diagnosis after a test or two, tell the patient what is wrong, give a prognosis, and administer a cure. Sometimes, in endocrinology, this works rather seamlessly. But biology and disease, especially diabetes, rarely function in this way. There are many uncertainties.

Science—similar to art, philosophy, literature, and economics—cycles through enthusiasms. These fashions are not simply based on predilections or taste; they are dictated by some political motivation, but mainly by what Sir Peter Medawar called “the art of the soluble.” In the seventeenth and eighteenth centuries, mathematics and astronomy were the thriving sciences because funding was available for solutions that were attainable. In particular, descriptive astronomy was important as a means of navigation, navigation was important as a means of keeping ships safely at sea, and ships at sea were important for power.

Today, the largest area of scientific endeavor is in the biological sciences because medicine and health are high on the political agenda, and solutions are forthcoming in return for investment.

So, nearly a decade ago, there was much excitement about the mapping of the human genome.1 This was a classic example of “can-do” science, delivered ahead of many of the predictions. It was an extraordinary triumph. Written in this typeface in a single line it would stretch from London to Istanbul. But by itself it did not deliver answers to many therapeutic questions. It had been likened to the dawn of scientific anatomy at the time of Vesalius in the early renaissance. The analogy was good, because anatomy is the backbone of physiology and therapeutics, but it does not deliver any solutions by itself. Stranded on a desert island with a wiring diagram of a television would neither help one build a television nor mend one. Genomics and proteomics depend on understanding the mechanisms—the etiology, physiology, and pathology of disease—before one can hope to deliver practical therapeutics.

And, of course, the handbook or wiring diagram is always helpful—but only if you have other knowledge. There is a widespread perception that we have knowledge in medicine, and that therefore “things can be fixed.” If we know the genome, then we have the handbook of the human machine. Good doctors should therefore be able to make a diagnosis after a test or two, tell the patient what is wrong, give a prognosis, and administer a cure. Sometimes, in endocrinology, this works rather seamlessly. A patient is tired and intolerant of the cold. The physician measures the thyroid-stimulating hormone which is twice normal, tells the patient that they have hypothyroidism, prescribes thyroxine and all is well. Cause → diagnosis → therapy → cure. This can be characterized as a Newtonian approach. Newtonian physics seems rather invariant. Levers work very reproducibly. Calculate the rotational force on the fulcrum and the lifting power can be calculated exactly.
But biology and disease, especially diabetes, rarely function in this way. There are many uncertainties. We characterize patients as having “type 2 diabetes,” knowing that this is not a single entity. We struggle with degrees of insulin resistance and β-cell failure; we note macrovascular and microvascular disease; we measure surrogate markers for renal disease; we photograph the eyes; we give advice on diet and lifestyle, knowing that these may only be partially relevant or partially acceptable to patients; we have patients who don’t mind injections and those that faint at the thought; we have young and old patients; we have clever and less astute patients; and finally, we have a wide armamentarium of drugs—each with their own benefits, side effects, and disadvantages—and we puzzle about which ones to use.

So where there is a puzzle or doubt we undertake trials. They will tell us whether agent A is better than B, whether agent C causes cancer, and whether patients taking D live longer than those taking E. And certainly trials are essential if we are not going to waste huge resources on agents of little or no use. So trials tell us what does work. We are sure in that tuberculosis can, usually, be eliminated by triple therapy, that angiotensin-converting enzyme inhibitors lower blood pressure and can improve longevity, and that peptic ulceration is often caused by Helicobacter pylori and can be treated with a one-week course of antibiotics. These are triumphs of research and the accumulation of evidence. But there are problems with the evidence of randomized controlled trials (RCTs)—even when the therapeutic benefit of one agent against another is demonstrated. These are the problems:

- The choices available to a physician are never properly represented in a trial. Type 2 diabetes, after metformin therapy, is clearly not a useful agent!
- Drugs may not be available to the physician.
- Drugs used in previous trials may now no longer be prescribed or available or thought to be appropriate.
- The therapeutic choices may be dictated by cost rather than efficacy. A wonderful agent that is too expensive to use going to waste huge resources on agents of little or no use.
- The US and European regulators take different views about pharmaceutical agents, so there cannot be an agreed clinical view that has transatlantic credence, much less a global one.
- So where there is a puzzle or doubt we undertake trials. They will tell us whether agent A is better than B, whether agent C causes cancer, and whether patients taking D live longer than those taking E. And certainly trials are essential if we are not going to waste huge resources on agents of little or no use. So trials tell us what does work. We are sure in that tuberculosis can, usually, be eliminated by triple therapy, that angiotensin-converting enzyme inhibitors lower blood pressure and can improve longevity, and that peptic ulceration is often caused by Helicobacter pylori and can be treated with a one-week course of antibiotics. These are triumphs of research and the accumulation of evidence. But there are problems with the evidence of randomized controlled trials (RCTs)—even when the therapeutic benefit of one agent against another is demonstrated. These are the problems:

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So guidelines when presented as algorithms are flawed, not in their generality, but in their specificity. This has been recog-

**Selected Abbreviations and Acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>ACCORD</td>
<td>Action to Control CardiOvascular Risk in Diabetes</td>
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<td>ADVANCE</td>
<td>Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation</td>
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<tr>
<td>HbA1c</td>
<td>glycated hemoglobin</td>
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<td>RCT</td>
<td>randomized controlled trial</td>
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<td>UKPDS</td>
<td>United Kingdom Prospective Diabetes Study</td>
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In the latest position statement of the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA), the two associations formed a joint statement that explicitly recognized the complexity and the necessity for context within the decision-making process. In particular, they recognized the centrality of the patient in the process of the treatment of type 2 diabetes and the need to think carefully if certain subsidiary aspects were considered important; the aspects they considered were the risk of hypoglycemia, the need for weight reduction, or the cost of the medications. They illustrate how the therapeutic decisions will embrace very different agents when these considerations are addressed. Such considerations are wider than these illustrated scenarios. Figure 1 shows how, within the context of making clinical decisions bounded by the rigorous approach of RCTs, a clinician needs to be aware of a multitude of other factors. Some, or all of these, will, and should be, part of the strategy of diabetes care.

Treating type 2 diabetes is more than treating HbA1c to targets. It does need knowledge and an understanding of interventional trials. But it also needs skill, engagement with patients, and, in particular, wisdom.

**References**


**Keywords:** decision-making process; Newtonian approach; randomized controlled trial; type 2 diabetes
ÉDITORIAL

Le fait de considérer que nous disposons de connaissances en médecine et donc que “les choses peuvent être réparées” est une opinion répandue. Le génome étant le manuel de la machine humaine, les bons médecins devraient pouvoir d’établir un diagnostic, indiquer aux patients ce qui ne va pas, donner un pronostic et prescrire un traitement. Parfois, en endocrinologie, cela se fait relativement sans heurt... Mais certaines pathologies, comme le diabète, fonctionnent rarement de cette manière.”

Traitement du diabète de type 2 : décalage entre la perception et les preuves

par D. R. Matthews, Royaume-Uni

L a science – comme l’art, la philosophie, la littérature et l’économie – présente des cycles d’enthousiasme. Ces modes ne sont pas seulement basées sur des préférences ou le goût ; elles sont parfois dictées par des motivations politiques, mais essentiellement par ce que Sir Peter Medawar appelait « l’art du soluble ». Aux XVIIe et XVIIIe siècles, les mathématiques et l’astronomie étaient des sciences florissantes car il existait des financements pour des solutions accessibles. En particulier, l’astronomie descriptive était importante comme moyen de navigation, la navigation était importante pour maintenir les bateaux sur la mer de façon sûre, et les bateaux sur la mer étaient importants pour la puissance. Aujourd’hui, c’est sur les sciences biologiques que se concentrent les principaux efforts scientifiques, la médecine et la santé étant en haut de l’ordre du jour politique, et les solutions faciles à obtenir pour un retour sur investissement.

Ainsi, il y a près d’une décennie, le séquençage du génome humain a suscité un intérêt considérable. Il s’agissait d’un exemple classique de la science “toute puissante”, dont les résultats ont dépassé un grand nombre de prédictions. Cela a été un triomphe extraordinaire. S’il était écrit avec cette police de caractères sur une ligne unique, il s’étendrait de Londres à Istanbul. Toutefois, il ne répond pas en lui-même à de nombreuses questions thérapeutiques. Il a été comparé à l’aube de l’anatomie scientifique au temps d’André Vésale au début de la Renaissance. L’analogie est intéressante, car l’anatomie est le pilier de la physiologie et de la thérapeutique, mais ne fournit aucune solution par elle-même. Échoué sur une île déserte avec le schéma de montage d’une télévision n’aidera ni à en construire une ni à en réparer une. La génomique et la protéomique dépendent de la compréhension des mécanismes – l’étiologie, la physiologie et la pathologie des maladies – avant que l’on puisse espérer proposer des traitements adaptés.

Et, bien entendu, le manuel ou le schéma de montage est toujours utile – mais uniquement si vous avez d’autres connaissances. Considérer que nous disposons de connaissances en médecine et donc que « les choses peuvent être réparées » est une opinion répandue. Si nous connaissions le génome, nous avons donc le manuel de la machine humaine. Les bons médecins devraient donc être en mesure d’établir un diagnostic après un test ou deux, indiquer aux patients ce qui ne va pas, donner un pronostic et prescrire un traitement. Parfois, en endocrinologie, cela se fait relativement sans heurt. Un patient est fatigué et intolérant au froid. Le médecin fait doser l’hormone thyroïdienne dont la valeur est le double de la normale, il indique au patient que celui-ci souffre d’une hypothyroïdie, il prescrit de la thyroxine et tout s’arrange. Cause → diagnostic → traitement → guérison. Cela peut
être caractérisé d’approche newtonienne. La physique newtonienne semble relativement immuable. Les leviers fonctionnent de manière très reproductible. Calculer la force de rotation sur un pivot et la force de levage peut être effectuée de manière exacte.

Mais la biologie et les pathologies, notamment le diabète, fonctionnent rarement de cette manière. Il existe de nombreuses incertitudes. Nous caractérisons les patients comme atteints d’un « diabète de type 2 », en sachant qu’il ne s’agit pas d’une entité unique. Nous nous efforçons de lutter avec les différents degrés d’insulinorésistance et le déficit des cellules β ; nous notons l’existence d’une maladie macrovasculaire et microvasculaire ; nous mesurons les marqueurs de substitution pour la maladie rénale ; nous photographions les yeux ; nous donnons des conseils sur l’alimentation et le style de vie, en sachant qu’ils ne sont pas totalement pertinents ou acceptables pour les patients ; certains de nos patients supportent parfaitement les injections et d’autres perdent connaissance à la simple pensée d’une aiguille ; nous avons des patients jeunes et des patients âgés ; nous avons des patients intelligents et des patients moins brillants ; et enfin, nous disposons d’un large arsenal de médicaments – chacun d’eux ayant ses propres avantages, effets indésirables et inconvenients – et nous nous interrogeons sur ceux à utiliser.

Lorsqu’il existe une interrogation ou un doute, nous menons des études. Elles nous disent si l’agent A est meilleur que B, si l’agent C provoque un cancer et si les patients traités par D vivent plus longtemps que ceux prenant E. Les études sont certainement essentielles si nous ne voulons pas dilapider des ressources considérables ou utiliser des médicaments ne présentant que peu ou pas d’intérêt. Aussi les études nous disent si E ne fonctionne pas – par exemple, la vitamine E, dans l’étude HOPE (Heart Outcomes Prevention Evaluation), l’étude ACCORD (Action to Control Cardiovascular Risk in Diabetes) et l’étude ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation) bien que l’étude UKPDS ait recruté des nouveaux cas de diabète sans complications manifestes ou d’antécédents récents d’événements médicaux, tandis que l’étude ACCORD a recruté des patients atteints de diabète depuis près de 10 ans (comme l’étude ADVANCE) présentant des risques établis de maladies cardio-vasculaires.

Les conclusions peuvent ne pas être généralisables à un éventail de patients plus large que les critères d’inclusion de l’ECR. Ces critères peuvent être limités par les paramètres suivants :

- L’hémoglobine glyquée (HbA1c) est comprise entre certaines limites : les pathologies les plus sévères et les plus bénéfiques sont généralement exclues.
- L’âge des patients est compris entre certaines limites : les patients les plus âgés sont souvent exclus.
- Origine : les patients japonais répondent différemment des patients occidentaux, et ces deux populations présentent des différences par rapport aux patients d’Afrique noire.
- Sexe : les femmes sont parfois exclues ou pratiquement exclues. L’étude VADT (Veterans Affairs Diabetes Trial) a été presque entièrement effectuée chez des patients masculins.

Tous les compte-rendus d’études présentent les moyennes ou les médianes des réponses. Dans un essai particulier, certains patients répondent très bien et d’autres pas du tout. Les raisons en sont multiples : un patient peut ne pas respecter le schéma thérapeutique ; le diagnostic peut avoir été erroné (le patient peut être porteur d’une variante génétique) ; l’absorption peut être meilleure chez certains patients ; parfois les effets indésirables limiteront la capacité thérapeutique.


Les ECR sont souvent sponsorisées par des laboratoires pharmaceutiques. Ces sociétés reconnaissent que la supériorité de leur médicament pourra être démontrée contre certains produits (et non d’autres) et que leur choix est ainsi soigneusement planifié.

Les choix thérapeutiques peuvent être dictés par les coûts plutôt que par l’efficacité. Si un médicament extraordinaire est trop coûteux pour être utilisé, il n’est manifestement pas utile !
Les médicaments peuvent ne pas être disponibles pour le médecin.

Les médicaments utilisés dans des études précédentes peuvent ne plus être prescrits ou disponibles ou encore considérés comme appropriés.

Les agences réglementaires américaine et européenne ont des avis différents sur les produits pharmaceutiques, il ne peut donc y avoir de consensus clinique transatlantique, et encore moins mondial.

De même, les directives présentées sous forme d’algorithmes sont impartiales, non pas dans leur généralité, mais dans leur spécificité. La dernière prise de position de l’Association européenne pour l’étude du diabète (European Association for the Study of Diabetes, EASD) et de l’Association américaine du diabète (American Diabetes Association, ADA) l’atteste'. Les deux associations ont formulé une déclaration commune reconnaissant explicitement la complexité et la nécessité de prendre en compte le contexte dans le processus de prise de décision. En particulier, elles ont reconnu l’importance centrale du patient dans le processus thérapeutique du diabète de type 2 et la nécessité d’examiner soigneusement l’importance de certains aspects secondaires dont le risque d’hypoglycémie, la nécessité de réduction du poids ou le coût des médicaments. Cela illustre la façon dont les décisions thérapeutiques englobent des médicaments très différents lorsque ces facteurs sont pris en compte. Des considérations de ce type sont plus larges que les scénarios illustrés.

La Figure 1 montre comment, dans le contexte de la prise de décision clinique encadrée par l’approche rigoureuse des ECR, un médecin doit être conscient d’une multitude d’autres facteurs. Certains, si ce n’est tous, constituent ou doivent constituer une partie de la stratégie des soins antidiabétiques.

Diabetes has reached epidemic proportions throughout the world. There is, however, strong evidence that the diabetes burden can be reduced by improving diabetes management. Despite this, the care received by many people with diabetes is less than optimal worldwide. Guidelines are an essential tool for addressing this situation. The International Diabetes Federation (IDF) has developed global guidelines including a treatment algorithm for people with type 2 diabetes. Limitations in the evidence base mean that recommendations and guidance are best described as evidence-informed consensus. While there is an extensive range of blood glucose-lowering therapies, availability and cost limits access to many of these options in many middle- and low-income countries. IDF guidance balances these important considerations with efficacy and safety. The usual approach recommended in the IDF algorithm is use of metformin as first-line therapy followed by a sulfonylurea when a second agent becomes necessary, and moving to a third oral agent or insulin if glycemic targets are not achieved. The generic IDF treatment algorithm is not proscriptive, but rather is formulated as a template for local adaptation by individual countries which do not have their own algorithms.

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The translation of guidelines into everyday practice remains a challenge. Many approaches have been used with varying success, but the most effective are multidimensional and locally specific. Greater support is needed for guideline implementation. Plans for implementation should be developed at the same time as the guidelines are being formulated and should be considered an integral part of the planning stage of guideline development.”

Type 2 diabetes
recommendations: the move toward an evidence-informed consensus

by S. Colagiuri, Australia

Diabetes has reached epidemic proportions and is a major global burden, especially in developing countries.1 Type 2 diabetes is associated with significant morbidity and decreased life expectancy due to its complications, which include heart disease, stroke, amputation, blindness, and kidney failure. It diminishes quality of life, impacts on employment and life opportunities, and has wide-ranging economic implications for the individual, the family, and society. There is considerable evidence that the diabetes burden can be reduced by improving diabetes management. Despite the available evidence, the care received by many people with diabetes is less than optimal worldwide.2 Guidelines are an essential tool for addressing this situation. A focus of the International Diabetes Federation (IDF) is to provide globally relevant guidance to improve the quality and consistency of diabetes care through the development and implementation of guidelines.

The evidence framework
Diabetes care is complex, involving a range of interventions, including education, lifestyle modification (diet, physical activity), medications for control of blood glucose and risk factors for cardiovascular disease, and ongoing monitoring and review. Ide-
ally, intervention, especially pharmacotherapy, would be based on demonstrating a benefit in reducing morbidity and premature mortality; however, few interventions have data on these end points. Instead, potential benefits are based on demonstrating a favorable effect on improving intermediate outcomes, such as lowering glycated hemoglobin (HbA1c). Any benefits should be balanced against the occurrence of undesirable effects, including hypoglycemia, weight gain, and treatment side effects. Other considerations that are important from an IDF perspective include availability and cost of therapies. On an individual level, clinical decision making requires more than just taking into account efficacy of a particular treatment. Factors which influence the treatment used in a particular patient include contraindications, potential side effects, patient preference, local availability and prescribing restrictions, and cost to the individual and health care system.

The benefits of intervention

The UKPDS (United Kingdom Prospective Diabetes Study) demonstrated that tighter blood glucose control reduced complications in people with newly diagnosed type 2 diabetes. The intensively treated group had significantly fewer microvascular complications and lower incidence of the composite end point compared with the conventionally treated group. The Kumamoto study confirmed the benefits of intensive treatment in reducing the development or progression of microvascular complications. Microvascular benefits of improved glycemic control were also shown in ACCORD (Action to Control CardiOvascular Risk in Diabetes study), ADVANCE (Action in Diabetes and Vascular disease: Preter-Ax and DiamicroN MR Controlled Evaluation), and the VADT (Veterans Affairs Diabetes Trial). These studies failed to show a benefit on macrovascular complications. In the ACCORD study, two secondary outcomes were significant: an increase in mortality and a decrease in nonfatal myocardial infarction were observed in the intensively treated group. However, a subsequent meta-analysis incorporating these major studies showed a significantly reduced risk of major cardiovascular events and myocardial infarction, but no reduction in all-cause mortality or cardiovascular death.

The benefits of multifactorial intervention were demonstrated in the Steno-2 study. Subjects in the intensive therapy group received multifactorial treatment including behavior modification and pharmacological therapy for hyperglycemia, hypertension, and dyslipidemia, while the conventional group was treated according to national guidelines. Intensive therapy significantly reduced cardiovascular disease, nephropathy, retinopathy, and autonomic neuropathy by about 50%. The benefits of intervention are observed not only during the study period, but also continue for several years after the intensive intervention—the so-called legacy effect. In the UKPDS posttrial monitoring study, subjects were observed for up to 10 years. In the sulfonylurea/insulin groups, risk reduction persisted at 10 years for any diabetes-related end point and microvascular disease, and significant risk reductions for myocardial infarction and death from any cause emerged over time. In the metformin group, significant risk reductions persisted over the 10 years. In the Steno-2 study, by 5 years’ post intervention, a significant reduction in risk of death in the intensively treated group emerged compared with usual care.

Choosing a pharmacological intervention

The range of pharmacological agents for the control of blood glucose continues to increase. The evidence base for deciding on a particular treatment or combination is limited by a lack of evidence directly comparing many of the choices. For example, if metformin is accepted as first-line pharmacotherapy, as advocated by many guidelines, and a second agent is required, then there are six therapeutic classes of blood glucose-lowering agents from which to choose: sulfonylureas (including glinides), α-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RA), and insulin. If adequate glucose control is not achieved and a third agent is required, there are five classes of agents from which to choose. This means there are 30 therapeutic options (6 × 5) for triple therapy. The options increase dramatically if different agents in each class are taken into account. There are at least three different types of sulfonylureas, four DPP-4 inhibitors, two GLP-1 RAs, and three broad insulin regimens, ie, 2160 (30 x 3 x 4 x 2 x 3) possible combinations for triple therapy, and clearly not all of these have been compared. It is encouraging that with the newer classes of agents a broader approach is being used to undertake direct comparative studies.

Most of the data relating to pharmaceutical interventions are based on efficacy in improving blood glucose, which is generally similar between agents, depending on whether the agent is used as first-, second-, or third-line therapy. Therefore, ultimately, individual treatment choices are more often based on other considerations. These include unwanted consequences such as risk of hypoglycemia and weight gain, which are inevitable with insulin, but differ between other agents and between studies. Cost to the individual, the health care system, and society is an important consideration, and cheaper, well-established, and efficacious treatments (eg, metformin and sulfonylureas) continue to be widely used and recommended in guidelines globally.

The IDF approach

The IDF is an umbrella international nongovernmental organization of over 200 national diabetes associations in over 160 countries and has been leading the global diabetes community since 1950. The IDF’s mission is to promote diabetes care, prevention, and a cure worldwide.

The IDF Clinical Guidelines Task Force focuses on developing guidelines and clinical care recommendations which are globally relevant. Clinical management guidelines are a routine
part of clinical practice and are an essential starting point for improving clinical care. Their recommendations synthesize the evidence to identify practices and processes of diabetes care that lead to better outcomes. Similarly, guideline recommendations establish standards and benchmarks that can assist policy makers to allocate resources judiciously and assess the need for services and workforce development to achieve desired standards of care and, ultimately, improved health outcomes.13

**Evidence-informed consensus**

Developing guidelines, including treatment algorithms, is complex for several reasons. While guideline recommendations are based on best available evidence, it is clear that treatment guidance cannot be truly evidence-based because of a lack of studies comparing all available options of treatment combination. Because of this limitation, IDF guidance is best described as evidence-informed consensus which seeks to balance available evidence with other important individual, practical, and societal considerations.

**“Levels of care” approach**

All people with diabetes should have access to the broad range of diabetes services and therapies, and no person should be denied any element of effective diabetes care. However, it is recognized that in many parts of the world, the implementation of particular standards of care is limited by lack of resources. The IDF has developed a practical approach to promote the implementation of cost-effective evidence-informed care in settings between which resources vary widely. The approach adopted by the IDF has been to give advice according to three levels of care.13

**Recommended care** is evidence-based care which is cost-effective in most countries with a well-developed service base, and with health care funding systems consuming a significant part of national wealth. Recommended care should be available to all people with diabetes and the aim of any health care system should be to achieve this level of care. However, in recognition of the considerable variations in resources throughout the world, other levels of care are described which acknowledge low- and high-resource situations.

**Limited care** is the lowest level of care that anyone with diabetes should receive. It acknowledges that standard medical resources and fully trained health professionals are often unavailable in poorly funded health care systems. Nevertheless, this level of care aims to achieve with limited resources a high proportion of what can be achieved by recommended care.

**Comprehensive care** includes the most up-to-date and complete range of health technologies that can be offered to people with diabetes, with the aim of achieving best possible outcomes. However, the evidence base supporting the use of some of these expensive or new technologies is relatively weak.

**IDF treatment algorithm**

The generic IDF treatment algorithm (Figure 1, page 12)13 takes into consideration available evidence and differences in global availability, access, and cost of medications.13 The algorithm is not prescriptive, but rather is formulated as a template for local adaptation by individual countries which do not have their own algorithms. The algorithm will be continuously updated as new evidence, particularly the results of current outcomes studies, becomes available.

**Usual and alternative approaches to therapeutic choice**

There is a wide range of blood glucose-lowering agents; however, availability and access to many of these is limited in many middle- and low-income countries. Treatment algorithms are intended to provide guidance on ways in which these therapies can be used either alone or in combination. The IDF algorithm is structured to provide a stepwise approach to intensifying therapy if blood glucose targets are not met. It also provides advice on what is considered a usual or alternative approach to selecting a therapy. The usual approach represents therapies which would usually be chosen first unless contraindicated. These therapies are effective, safe, relatively inexpensive, and widely available globally. The alternative approach indicates other therapeutic options which could be used if the usual approach therapies are contraindicated, not tolerated, or not considered suitable for a particular individual.

Lifestyle changes, including diet modification, increase in physical activity, weight reduction in those that are overweight, and smoking cessation, are essential components of the management of type 2 diabetes. This is recommended as the initial step in diabetes management. Subsequent treatment changes are based on failure to achieve target HbA1c, after a 3-month period, taking into account tolerability and hypoglycemia. A recent systematic review compared effectiveness and safety of medications for type 2 diabetes, excluding α-glucosidase inhibitors and insulin.15 This review was limited by the lack of comparative studies allowing a comprehensive comparison of all medication classes and outcomes, especially newer agents. Most diabetes medications were similarly efficacious when used as monotherapy and decreased HbA1c levels by 1%
Although considered as a class, there may be intrinsic differences between the various sulfonylureas. Schramm et al. examined mortality and cardiovascular risk associated with available insulin secretagogues compared with metformin in a nationwide Danish study. All-cause mortality, cardiovascular mortality, and a composite end point with the different medications were assessed over a median 3.3 years of follow-up. Compared with metformin, glimepiride, glibenclamide, gliclazide, and tolbutamide were associated with increased all-cause and cardiovascular mortality and increased incidence of the composite end point. Overall outcomes for gliclazide and repaglinide were not different from metformin. In addition, rates of hypoglycemia vary with different sulfonylureas, being lowest with gliclazide. These differences in rates of hypoglycemia are reflected in clinical trials comparing sulfonylureas and DPP-4 inhibitors added to metformin, and during fasting associated with Ramadan, in which gliclazide is associated with less hypoglycemia.

α-Glucosidase inhibitors are widely used and popular in many, especially Asian, countries. Hanefeld et al. performed a meta-analysis on the effect of the α-glucosidase inhibitor acarbose on cardiovascular events in seven randomized, placebo-controlled studies of at least 52 weeks’ duration and found significantly reduced risk for myocardial infarction and any cardiovascular event.

When monotherapy fails to achieve target glycemia, a second agent is required. Of the many options, the IDF recommends the addition of a sulfonylurea as the usual approach for people taking metformin. The alternative approach is to

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**Figure 1. The IDF treatment algorithm.**

use an α-glucosidase inhibitor, a DPP-4 inhibitor, or a thiazolidinedione. Combination therapy decreases HbA1c levels more than monotherapy by about 1% (11 mmol/mol). A recent network meta-analysis compared blood glucose–lowering therapies added to metformin in short-term studies. Of the IDF second-line therapies, sulfonylureas and thiazolidinediones showed greater reductions in HbA1c than α-glucosidase inhibitors and DPP-4 inhibitors. Considering other relevant factors such as availability and cost, combined metformin and sulfonylurea therapy remains an effective and safe treatment which is widely used throughout the world.

Alternative second-line therapies include an α-glucosidase inhibitor or DPP-4 inhibitor. Both are effective when used in combination with metformin (or sulfonylurea) and lower HbA1c by approximately 0.7% (8 mmol/mol), have a low risk of hypoglycemia, and have favorable effects on weight. Thiazolidinediones effectively lower blood glucose, but their side effects and increasing safety concerns have seen their use decrease. Adverse effects include weight gain and fluid retention, which may result in peripheral edema and congestive heart failure. Increasingly recognized is the greater incidence of fractures, especially in females. Some regulatory authorities have acted in relation to possible adverse cardiovascular effects with rosiglitazone and a possible link with bladder cancer with pioglitazone. Although thiazolidinediones are included as an option in the IDF algorithm, other choices are favored.

If diabetes control remains unsatisfactory and a third agent is required, the usual approach options include either adding a third oral agent or commencing insulin. Options for a third oral agent include a DPP-4 inhibitor, an α-glucosidase inhibitor, or a thiazolidinedione. Few studies have compared adding a third agent or using insulin, but those which have show similar short-term effects on glycosmic control.

The efficacy of add-on blood glucose–lowering therapy in people with type 2 diabetes not controlled with metformin and a sulfonylurea was recently analyzed in randomized trials of at least 24 weeks’ duration. Compared with placebo, medication classes did not differ in effect on HbA1c level with reductions ranging from 0.7% (7 mmol/mol) with acarbose to 1.1% (12 mmol/mol) with insulin. Weight increase was seen with insulins and thiazolidinediones, and insulin resulted in twice the absolute number of severe hypoglycemic episodes compared with noninsulin blood glucose–lowering therapies.

The UKPDS established the effectiveness of intensive therapy based on insulin treatment in reducing vascular complications compared with conventional therapy. Insulin options include adding once-daily basal insulin or twice-daily premixed insulin, usually in combination with oral blood glucose–lowering medications. While there is ongoing debate about these two approaches, a recent systematic review reported the percentage of people reaching an HbA1c target of <7.0% (53 mmol/mol) was similar. However, there was considerable heterogeneity between study results related to final insulin dose and use of oral medications; overall incidence of hypoglycemia was variable, but weight gain was less with basal insulin. The IDF algorithm lists GLP-1 RAs as an alternative third-line approach mainly on the basis of their limited global availability and their cost. GLP-1 RAs lower HbA1c by approximately 1% (11 mmol/mol) compared with placebo, and result in moderate and continuous weight loss and low rates of hypoglycemia, but are associated with gastrointestinal side effects, especially nausea and vomiting. There are some poorly supported data that the use of GLP-1 RAs may predispose to pancreatitis.

The final step in the algorithm is to intensify insulin therapy with basal and mealtime insulins. Intensified insulin therapy in type 2 diabetes has been shown to improve metabolic control and improve clinical outcomes.

Guideline implementation

The translation of guidelines into everyday practice remains a challenge. Many approaches have been used with varying success, but the most effective are multidimensional and locally specific. Support is needed for guideline implementation. Plans for implementation should be developed at the same time as the guidelines are being formulated and should be considered an integral part of the planning stage of guideline development.

The author has received fees for participating in advisory boards or speaking engagements from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GliaxoSmithKine, Merck & Co, Novartis, Novo Nordisk, Roche Diagnostics, and Servier.

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Type 2 Diabetes: Evidence Beyond Perception

The diabète a pris des proportions épidémiques à travers le monde. Il est cependant prouvé qu’on peut en réduire les conséquences par l’amélioration de sa prise en charge. Pourtant, les soins reçus par de nombreuses personnes dans le monde sont loin d’être optimaux. Les recommandations constituent un outil essentiel pour améliorer cette situation. La Fédération Internationale du Diabète (IDF) a établi des recommandations mondiales qui comprennent un algorithme de traitement pour les diabétiques de type 2. Les prescriptions ayant leurs limites, les recommandations et les directives sont en fait un consensus fondé sur des preuves. Alors qu’il existe un large éventail de traitements visant à contrôler la glycémie, de nombreux pays à faibles et moyens revenus n’y ont pas accès à cause de leur coût élevé et de leur disponibilité limitée. Dans ses recommandations, l’IDF doit donc tenir compte aussi bien de ces préoccupations importantes que de l’efficacité et de la sécurité d’emploi des médicaments. L’algorithme de l’IDF recommande habituellement l’utilisation de la metformine en traitement de première intention, suivie de celle d’une sulfonylurée quand un deuxième médicament devient nécessaire, et l’administration d’une troisième molécule par voie orale ou d’insuline si les objectifs glycémiques ne sont pas atteints. L’algorithme thérapeutique générique de l’IDF n’est pas normatif ; il a été conçu comme un modèle à adapter localement par les pays ne possédant pas leurs propres algorithmes.

Keywords: evidence-informed consensus; guidelines; International Diabetes Federation; treatment algorithm; type 2 diabetes

Le diabète de type 2 est devenu une épidémie mondiale. Il est cependant prouvé qu'on peut en réduire les conséquences par l'amélioration de sa prise en charge. Cependant, les soins reçus par de nombreuses personnes dans le monde sont loin d'être optimaux. Les recommandations constituent un outil essentiel pour améliorer cette situation. La Fédération Internationale du Diabète (IDF) a établi des recommandations mondiales qui comprennent un algorithme de traitement pour les diabétiques de type 2. Les prescriptions ayant leurs limites, les recommandations et les directives sont en fait un consensus fondé sur des preuves. Alors qu'il existe un large éventail de traitements visant à contrôler la glycémie, de nombreux pays à faibles et moyens revenus n'y ont pas accès à cause de leur coût élevé et de leur disponibilité limitée. Dans ses recommandations, l'IDF doit donc tenir compte aussi bien de ces préoccupations importantes que de l'efficacité et de la sécurité d'emploi des médicaments. L'algorithme de l'IDF recommande habituellement l'utilisation de la metformine en traitement de première intention, suivie de celle d'une sulfonylurée quand un deuxième médicament devient nécessaire, et l'administration d'une troisième molécule par voie orale ou d'insuline si les objectifs glycémiques ne sont pas atteints. L'algorithme thérapeutique générique de l'IDF n'est pas normatif ; il a été conçu comme un modèle à adapter localement par les pays ne possédant pas leurs propres algorithmes.

Keywords: evidence-informed consensus; guidelines; International Diabetes Federation; treatment algorithm; type 2 diabetes
Recent results from large randomized clinical trials (RCTs) started a new wave of discussion on approaches to glucose-lowering treatment of type 2 diabetes (T2D). Differing results prompted experts to discuss underlying reasons; one particular focus was the increased cardiovascular mortality in the ACCORD trial (Action to Control CardiOvascular Risk in Diabetes), which remains unexplained. Such concerns justify a more in-depth search for explanations behind the controversial results. One possible factor is the sulfonylurea (SU) used: gliclazide only, as in ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation), or gli- mepiride only, as in ACCORD and the VADT (Veterans Affairs Diabetes Trial). Nowadays, it is believed that high-quality observational studies may extend evidence over a wider population and are likely the best choice for identifying harms, or when RCTs are unethical or impractical. We should acknowledge a small number of RCTs that directly evaluate the effects of various SUs—in particular for direct comparisons of gliclazide and glibenclamide; nevertheless, the relevance of observational studies is increasing due to issues arising from comparative analysis of the latest megatrials. Observational studies, in particular those based on constantly growing primary care–based territorial registers, provide valuable information about the results of T2D treatment that can complement or clarify the results of RCTs. Pharmacoepidemiological analysis of T2D treatment results requires differential evaluation of individual SUs, rather than an overall generation-based assessment.

From randomized clinical trials to registry analysis: where is the evidence?

By M. D. Khalangot, Ukraine
ureas (SUs), proving the high level of distrust in the current model of T2D treatment, which has been used for the last decade. SU critics argue that out of five large RCTs—the UGDP (University Group Diabetes Program), the UKPDS (United Kingdom Prospective Diabetes Study), ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation), and the VADT (Veteran Affairs Diabetes Trial)—two trials (the UGDP and ACCORD) showed an increase in cardiovascular disease (CVD) events and mortality, and the others showed no reduction in CVD events and mortality in patients receiving OGLDs, except for a group of overweight T2D patients treated with metformin versus diet only in the framework of the UKPDS.

Several experts discussing all possible reasons for such differing results in the main trials came to no conclusion explaining the increased cardiovascular mortality in ACCORD despite a multitude of theories. However, we believe that there are only a few theories to explain differing results for T2D glucose-lowering treatment intensification: for example, with the UGDP, it may be insufficient initial randomization that led to differences in the occurrence of adverse outcomes in tolbutamide and placebo groups,23 and perhaps tolbutamide, a first-generation SU, was not the best choice, as second-generation SUs were shortly thereafter developed by the pharmaceutical industry.

ACCORD and ADVANCE trials, when compared, indicate quantitative differences in the use of insulin and thiazolidinediones.22 Indeed, differences in the frequency of severe hypoglycemia requiring medical assistance or with an impaired level of consciousness (%/year) (3.1% versus 1.0% and 0.7% versus 0.4%, in the intensive and standard treatment groups of ACCORD and ADVANCE, respectively) as well as corresponding changes in weight (kg) (+3.5 versus +0.4 and −0.1 versus −1.0 in ACCORD and ADVANCE, respectively) mentioned in these studies smoothly conform with a more frequent insulin use (77% and 41% in intensive groups of ACCORD and ADVANCE, respectively). However, in the VADT trial, even though insulin was used more often (90% versus 74% in the intensive treatment group and the standard treatment group, respectively), there was no increase in mortality in the intensive group of this trial. One explanation for increased mortality in the intensive group of ACCORD could be the faster lowering of hyperglycemia: in ACCORD, the target glycated hemoglobin level was achieved after 6 months; in ADVANCE and VADT, this took over 6 months.

Surprisingly, the retrospective epidemiological analysis of the ACCORD study showed that among participants who experienced an episode of severe hypoglycemia, the relative risk of death was lower in those in the intensive glycaemia treatment arm than in those in the standard treatment arm and the increased relative risk of mortality observed in the intensive treatment group in the ACCORD trial cannot be explained by severe hypoglycemia as it was measured in the study.12 We may suppose that unrecognized hypoglycemic episodes are one of many possible explanations for the increased mortality in ACCORD.

Is there a specific connection between mortality risk in T2D patients and various OGLDs, including second-generation SUs?

An apparent difference, regularly omitted by experts,22 between discussed large trials is in the SU used: gliclazide only (ADVANCE) or glimepiride only (ACCORD and the VADT). Both of these drugs are second-generation SUs that essentially differ pharmacodynamically and in their molecular mechanisms from tolbutamide (a first-generation SU which fell under suspicion due to the UGDP trial) and the still popular glibenclamide (glyburide), a second-generation SU. Thus, it seems that it is not the generation of the drug, but its qualities, including specificity for pancreatic β-cell, but not myocardial or vascular smooth muscle cell receptors, as well as noninterference in adaptation to ischemia (ischemic preconditioning) and extent of receptor bonding strength (reversibility) that determine the safety profile of a specific SU. Gliclazide and glimepiride are on equal footing in regard to the first two factors; however, when it comes to reversibility, gliclazide has an advantage.24-28 Gliclazide has additional beneficial qualities, such as antioxidant properties, which restore endothelial function, reduce platelet reactivity, and exert an anti-inflammatory effect.29-34

In the UKPDS, there was no difference in diabetes-related death or all-cause mortality between chlorpropamide (a first-generation SU) and glibenclamide (a second-generation SU),35 which identifies a need for further comparisons of safety among second-generation SUs. According to the hierarchy of clinical studies carried out within the last decade, RCTs and, especially, systematic reviews of several of these trials are traditionally considered gold standards for judging the benefits of

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**Selected abbreviations and acronyms**

ACCORD Action to Control Cardiovascular Risk in Diabetes
ADVANCE Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation
CAD coronary artery disease
CVD cardiovascular disease
HR hazard ratio
OGLD oral glucose-lowering drug
PROactive PROspective pioglitAzone Clinical Trial In macrovascular Events
RCT randomized clinical trial
T2D type 2 diabetes
UGDP University Group Diabetes Program
VADT Veterans Affairs Diabetes Trial
treatment, mainly because it is conceptually easier to attribute any observed effect to the treatments being compared.\textsuperscript{36,37} However, Pocock and Elbourne\textsuperscript{18} indicated that the search for corresponding RCTs in only the most prestigious journals can select a small, potentially atypical subgroup of available trials, which influences the quality of systematic reviews of these trials. A good example of this is the conclusion of a Canadian meta-analysis that glibenclamide indeed leads to more frequent hypoglycemia, compared with other sulfonylurea derivatives, but does not cause higher risk of cardiovascular events and mortality.\textsuperscript{39} This meta-analysis has been widely promoted in post-Soviet states, perhaps due to the fact that glibenclamide is the most frequently prescribed OGLD in these countries. It should be noted that the authors used the results of 21 RCTs for this meta-analysis, and only 3\textsuperscript{35,40,41} of those were used for evaluating cardiovascular events and mortality. Only 2 RCTs\textsuperscript{35,40} out of 3 that were the basis for the above meta-analysis compared the effect of glibenclamide with other sulfonylurea derivatives, which in fact did not include gliclazide. Consequently, the conclusions about glibenclamide’s safety\textsuperscript{35} are based on only 1 RCT (457 patients, one-year follow-up) that proved glimepiride is similar to glibenclamide in terms of metabolic control and tolerance.\textsuperscript{40}

Barton,\textsuperscript{37} in his comments on some current studies, states that “they do not justify a major revision of the hierarchy of evidence, but they do support a flexible approach in which [RCTs] and observational studies have complementary roles.” He believes that “high-quality observational studies may extend evidence over a wider population and are likely to be dominant in the identification of harms and when [RCTs] would be unethical or impractical.”\textsuperscript{37} Thus, observational studies are relevant, and their relevance increases with issues arising from comparative analysis of recent megatrials. This does not take away from the importance of a small number of RCTs that directly evaluate the effects of various SUs. This is particularly true for direct comparisons of gliclazide and glimepiride that are otherwise not likely to be found. This situation could be explained by ethical considerations.

**OGLD-related mortality risk in recent observational studies with some explanations for differing results**

Recent retrospective studies\textsuperscript{4-9} and one prospective\textsuperscript{11} cohort observational study compared CVD and/or mortality risk in T2D patients treated with different SU monotherapies\textsuperscript{5,7,11} or assessed mortality risk with different SU monotherapies or thiazolidinediones versus metformin.\textsuperscript{5,6,9} In retrospective observational cohort studies of a primary care–based diabetes register carried out in Ukraine, we evaluated risk of total and CVD mortality in a cohort of T2D patients that were treated with either gliclazide (n=50 341), glimepiride (n=2479), or gliclazide (n=11 368).\textsuperscript{8} Total mortality was lower for glimepiride and gliclazide versus the glibenclamide cohort: hazard ratios (HRs) were 0.33 (95% confidence interval [CI], 0.26-0.41; P<0.001) and 0.605 (95% CI, 0.413-0.886; P=0.01), respectively. CVD mortality risk reduction versus glibenclamide was significant only in the gliclazide cohort: 0.29 (95% CI, 0.21-0.38; P=0.001). Thus, glibenclamide treatment of T2D is associated with greater risk of all-cause mortality versus gliclazide or glimepiride treatment, and CVD mortality versus gliclazide treatment. Total mortality risk for those treated with glimepiride was higher than in those treated with gliclazide: HR=1.85 (95% CI, 1.19-2.90; P=0.006).\textsuperscript{5}

This observational, epidemiological primary care–based study revealed an adverse influence of glibenclamide in terms of higher general and cardiovascular mortality, compared with gliclazide, in the treatment of T2D patients, consistent with findings in studies by Johnsen et al\textsuperscript{42} and Monami et al.\textsuperscript{43} These latter studies, however, either touched upon the risk of myocardial infarction and related mortality,\textsuperscript{42} or were based on a much smaller cohort of patients.\textsuperscript{43} It is quite possible that a smaller patient cohort (568 patients), compared with the one used in our study (64 288 patients) allowed Monami et al to find a glibenclamide-associated age- and gender-adjusted mortality risk increase only for all-cause mortality, and not for CVD mortality.\textsuperscript{43} Glimepiride treatment is also linked to reduction in all-cause mortality, compared with glibenclamide treatment. However, we found no proof of CVD mortality reduction. Furthermore, the risk of all-cause mortality was significantly higher for glimepiride-treated patients, compared with gliclazide-treated ones.

Investigators from the French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction analyzed the outcomes of 1310 diabetic patients: among SU-treated patients, in-hospital mortality was lower in patients receiving gliclazide or glimepiride (2.7%), compared with glibenclamide (7.5%; P=0.019). The lower risk in patients receiving gliclazide/glimepiride versus glibenclamide persisted after multivariate adjustment (odds ratio 0.15; 95% CI, 0.04-0.56).\textsuperscript{11} These results seemed to be a convincing reason for Matthew C. Riddle to say goodbye to glibenclamide.\textsuperscript{17}

As I wrote earlier,\textsuperscript{44} in an article by Pantalone et al.,\textsuperscript{7} the authors did not identify an increased total mortality risk among individual SUs—glibenclamide versus glimepiride or glipizide—but did suggest that glimepiride may be the preferred SU in patients with a history of coronary artery disease (CAD). The authors found that in a retrospective cohort of patients with CAD, the HR for mortality in the subgroup of glibenclamide versus glimepiride was 1.36 (95% CI, 0.96-1.91; P=0.081).

Pantalone et al.\textsuperscript{7} refer to our assessment of total and cardiovascular mortality HRs in patients treated with gliclazide versus glibenclamide,\textsuperscript{4} considering them based on incorrect adjustment for variables. These authors estimated the HR for glipizide versus glyburide (glibenclamide), because glipizide and glimepiride are SUR1-specific (pancreatic-specific) sul-
fonylurreas, available and commonly used in the United States (gliclazide is not available in the United States). Meanwhile, the interaction of these molecules with the SU receptors is different; for example, their half-maximal inhibitory concentration on channel activity differs by more than 10 times, whereas the corresponding differences between glibenclamide, glipizide, and glimepiride could be significantly lower. Accordingly to a recent nationwide register–based study in Denmark, monotherapy with glibenclamide, glimepiride, or glipizide, but not with gliclazide, is associated with higher mortality and CAD risk compared with metformin. It is even speculated that differences between SUs may underpin the different outcomes observed in the ACCORD and ADVANCE trials.

In our study of 119,570 patients who had originally been assigned to monotherapy with glibenclamide, glimepiride, or gliclazide, the received treatment was confirmed to be unchanged in only 64,288 cases after a minimum of two follow-up checks. We managed to avoid bias in risk assessments that have arisen due to changes in treatment. This is why we have obtained gliclazide versus glibenclamide total and CVD mortality HRs that were so high that they have sustained adjustments for seven variables. The HR for glimepiride versus glibenclamide was not as high and was significant only for total mortality, without adjustment. We were unable to consider the influence of socioeconomic differences on the risk of SU-related mortality, but in the case of the glimepiride versus gliclazide comparison (HR 1.8; 95% CI, 1.2-2.9; P=0.006), this factor was not significant, as the cost for these drugs in Ukraine is the same.

It seems that Pantalone et al did not verify whether treatment remained unchanged during the observation period and did not mention the unadjusted HRs. The authors only provided HRs simultaneously adjusted for 22 variables, which greatly complicates the impact assessment of each variable. Furthermore, these authors indicated the need for prospective studies to assess the risk of individual SUs, but if gliclazide will not be included in such assessments, the truth will remain unrevealed. In reply to our comment, Pantalone et al confirmed that approximately 70% of the cohort remained on a single drug (baseline medication) throughout their time in the cohort, and believe that restricting an analysis to patients who continue the baseline drug throughout their duration in the cohort could create substantial bias.

This statement is partially true, as with increasing of the observation period, the selection factor may have a stronger influence on the results. On the other hand, only 70% (according to Ukrainian diabetic register data, only 50%) of the cohort remained on a single drug (baseline medication) throughout their time in the cohort, clearly lowering assessment accuracy. Retrospective analyses of large registers, that were based on primary care records and carried out in the United Kingdom and Denmark have avoided the lowering of assessment accuracy that can emerge due to changes in treatment. When creating regression models, these authors used an approach based on estimating the number of pharmacological “intervals,” in other words, periods of time during which there were no changes in treatment, or fixed 3-month periods.

Such an approach allowed comparing the risks of adverse treatment outcomes that would be definitely associated with the use of a particular OGLD. Metformin was considered the reference treatment in both trials. Unfortunately, in the British trial, SUs were categorized only as first- and second-generation drugs. This prevented comparison of mortality risks among second-generation SUs. Such comparison in the Danish study revealed significantly higher mortality risks in patients treated with glibenclamide, glimepiride, and glipizide, compared with metformin-treated ones, whereas there was no difference in mortality risk between gliclazide- and metformin-treated patients. Epidemiologists that analyzed the UK General Practice Research Database revealed an equal increase in total mortality risk for first- and second-generation SUs (versus metformin) and a decrease in such risk for thiazolidinediones. These data seem quite unexpected in light of a recent ban of rosiglitazone, and limitations laid down for pioglitazone (the latter is due to observational data from a French pharmacological register about an increase in bladder cancer in patients treated with pioglitazone); however, they are in agreement with confirmed data from the PROActive trial ([PROspective pioglitAzone Clinical Trial In macroVascular Events]; histologic diagnosis in one of the cases was reconsidered, leading to a statistical significance in differences between pioglitazone and control groups), and have been recently confirmed once again with retrospective analysis of the UK General Practice Research Database. Evaluation of the balance between increasing bladder cancer risk and decreasing macrovascular events risk associated with the use of pioglitazone in the treatment of T2D should be continued; however, today we must note that for pioglitazone we have data from the experimental trial PROActive and from observational retrospective assessments received from medical registers that are in agreement and are mutually complementary.

**Conclusion**

Observational studies, particularly those based on constantly growing primary care–based territorial registers provide valuable information on the results of T2D treatment that can complement or clarify the results of RCTs. Pharmacoepidemiological analysis of T2D treatment results requires a differential evaluation of individual SUs rather than an overall generation-based assessment. Such individual evaluation provides convincing arguments about the safe use of gliclazide, an SU extensively verified in RCTs.


Keywords: observational study; oral glucose-lowering drug; randomized clinical trial; type 2 diabetes

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**DES ÉTUDES CLINIQUES RANDOMISÉES À L’ANALYSE DE REGISTRES : OÙ EST LA PREUVE ?**

De récents résultats issus d’études cliniques randomisées (ECR) à grande échelle ont déclenché une nouvelle vague de débats sur les modalités des traitements visant à réguler la glycémie dans le diabète de type 2 (DT2). Des résultats divergents ont poussé les experts à en analyser les raisons sous-jacentes ; en particulier, l’augmentation de la mortalité cardiovasculaire dans l’étude ACCORD (Action to Control CardioVascular Risk in Diabetes), restée inexplicable, justifie une recherche plus approfondie visant à éclaircir ces résultats controversés. Le choix de la sulfonylurée (SU) utilisée peut entrer en ligne de compte : soit le gliclazide seul, comme dans l’étude ADVANCE (Action in Diabetes and Vascular disease : PreterAx and DiamicroN MR Controlled Evaluation), soit le glimepiride seul, comme dans les études ACCORD et VADT (Veterans Affairs Diabetes Trial). On pense aujourd’hui que des études observationnelles de haute qualité pourraient permettre d’étendre les preuves à des populations plus larges, et qu’elles sont vraisemblablement le meilleur choix pour identifier les risques, ou quand les ECR ne sont pas éthiques ou sont irréalisables. Si on peut reconnaître l’intérêt d’un petit nombre d’ECR évaluant directement les effets de plusieurs SU, en particulier par des comparaisons directes au gliclazide et au glibenclamide, l’importance des études observationnelles est néanmoins croissante en raison des problèmes dus à l’analyse comparative des études à grande échelle précédentes. Des études observationnelles, en particulier celles s’appuyant sur des registres de soins primaires territoriaux de plus en plus nombreux, fournissent des informations précieuses sur les résultats du traitement du DT2, qui peuvent compléter ou clarifier les résultats des ECR. L’analyse pharmacoépidémiologique des résultats du traitement du DT2 nécessite une évaluation différentielle de chaque SU, plutôt qu’une évaluation globale des différentes générations de traitement.
Asia is the “hotspot” for type 2 diabetes mellitus (T2DM)—all recent epidemiological studies continue to show rapid increases in prevalence occurring over a shorter time frame compared with other regions, with China and India having the largest number of people with diabetes. Apart from large numbers of people affected, it is also well-known that diabetes in Asia occurs in younger age groups and at a lower body mass index (termed the “metabolically obese” phenotype). With the younger age at onset, duration of disease is therefore longer, with higher risk of developing complications. Understanding which key pathophysiological abnormalities play major roles in triggering the development of T2DM will help clinicians make decisions on appropriate therapeutic agents. The important role of loss of β-cell mass and β-cell secretory dysfunction in the Asian diabetic individual makes the class of sulfonylureas (SUs) a clear choice either after metformin monotherapy failure or as first-line therapy in patients who are either intolerant of metformin or for whom metformin is contraindicated. The most recent guidelines (International Diabetes Federation 2011 and American Diabetes Association/European Association for the Study of Diabetes 2012) for the management of diabetes/hyperglycemia have continued to affirm the position of SUs. Gliclazide MR, as the agent used in ADVANCE (Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation), can therefore lay claim to having outcome data to support its clinical utility. The ADVANCE study includes a sizeable Asian cohort and as such, results and lessons learned can be directly applicable to the Asian T2DM patient.


Type 2 diabetes mellitus (T2DM), is known to cause premature death, largely via a two- to fourfold increase in macrovascular complications, in particular, cardiovascular mortality. The earlier the age of diabetes onset, the more years of life lost. Type 2 diabetes in Asians, as reported by the Asia-Pacific Cohort Studies Collaboration, is associated with similarly increased cardiovascular complications (Figure 1, page 22) as those reported from T2DM studies in white subjects. In an interim analysis of the UKPDS (United Kingdom Prospective Diabetes Study), an assessment of effect of ethnicity on incident fatal/nonfatal myocardial infarction (median follow-up 8.7 years) showed that despite having the lowest incidence of hypertension and current smoking, and being younger than their white and black counterparts, Asian Indian patients had a similar cardiovascular risk to whites.
In addition to the clinical consequences of T2DM, the unfortunate fact is that Asia has the highest burden of people with T2DM. Some of the world’s most populous countries are in Asia, including China, India, and Indonesia. Apart from sheer population sizes, the prevalence of T2DM in Asia has risen over a much shorter time, occurring in a younger age group (approximately 10-15 years younger than in whites) and in people with a lower body mass index (BMI).6

In the Asia-Pacific Cohort Studies Collaboration report,1 based on data from more than 93 000 people from China, Japan, Singapore, and Taiwan, Asian diabetic subjects had a lower mean BMI of 23.9 kg/m2, compared with nondiabetic subjects with a mean BMI of 22.1 kg/m2 (Table I).

This is in contrast to the higher BMIs noted in white T2DM subjects.

In Shaw’s review7 of current global estimates of T2DM burden, 5 of the top 10 countries for numbers of people aged 20-79 years with diabetes are from the Asia-Pacific region (Table II). These estimates are based on current prevalence rates of diabetes. The prevalence is increasing rapidly in many of these developing countries, driven by socioeconomic advancement, greater urbanization, as well as nutritional transition to overnutrition and sedentary lifestyle. A clear relationship between wealth of a country and burden of diabetes has been noted: as the average per capita consumption increases, a corresponding increase in diabetes prevalence is seen.

The majority of the projected increase is expected to come from developing countries such as those from the Asia-Pacific region. From 2010 to 2030, the numbers of diabetic people are projected to increase by 72% in South Asia and 47% in the Western Pacific region as opposed to 20% and 42% for

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**Figure 1.** Sex-, study-, and age-adjusted hazard ratios (log scale) for deaths from major cardiovascular diseases and all causes (diabetic vs nondiabetic), by age group.

*Abbreviations: CI, confidence interval; homog, homogeneity.*


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**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVANCE</td>
<td>Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>CYP</td>
<td>cytochrome P450</td>
</tr>
<tr>
<td>IGT</td>
<td>impaired glucose tolerance</td>
</tr>
<tr>
<td>MR</td>
<td>modified release</td>
</tr>
<tr>
<td>NGT</td>
<td>normal glucose tolerance</td>
</tr>
<tr>
<td>PM</td>
<td>poor metabolizer</td>
</tr>
<tr>
<td>SU</td>
<td>sulfonylurea</td>
</tr>
<tr>
<td>T2DM</td>
<td>type 2 diabetes mellitus</td>
</tr>
<tr>
<td>UKPDS</td>
<td>United Kingdom Prospective Diabetes Study</td>
</tr>
</tbody>
</table>

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**Table I.** Number of deaths/person-years and hazard ratios for diabetes vs nondiabetes, by age group.

<table>
<thead>
<tr>
<th>Disease</th>
<th>No diabetes</th>
<th>Diabetes</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>137/679</td>
<td>19/12</td>
<td>4.38 (2.63-7.31)</td>
</tr>
<tr>
<td>60-74</td>
<td>516/321</td>
<td>62/14</td>
<td>2.44 (1.84-3.22)</td>
</tr>
<tr>
<td>75+</td>
<td>638/58</td>
<td>42/22</td>
<td>1.57 (1.14-2.16)</td>
</tr>
<tr>
<td>(P homog&lt;0.0003)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>85/679</td>
<td>6/12</td>
<td>2.57 (1.00-6.59)</td>
</tr>
<tr>
<td>60-74</td>
<td>445/321</td>
<td>41/14</td>
<td>2.69 (1.91-3.80)</td>
</tr>
<tr>
<td>75+</td>
<td>552/58</td>
<td>25/22</td>
<td>1.30 (0.86-1.96)</td>
</tr>
<tr>
<td>(P homog=0.008)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cardiovascular disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>316/679</td>
<td>29/12</td>
<td>3.47 (2.30-5.21)</td>
</tr>
<tr>
<td>60-74</td>
<td>1359/321</td>
<td>127/14</td>
<td>2.27 (1.87-2.75)</td>
</tr>
<tr>
<td>75+</td>
<td>1710/58</td>
<td>91/22</td>
<td>1.49 (1.20-1.84)</td>
</tr>
<tr>
<td>(P homog&lt;0.0001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>1274/680</td>
<td>71/12</td>
<td>2.43 (1.89-3.12)</td>
</tr>
<tr>
<td>60-74</td>
<td>3761/323</td>
<td>309/14</td>
<td>1.78 (1.58-2.01)</td>
</tr>
<tr>
<td>75+</td>
<td>3643/59</td>
<td>219/22</td>
<td>1.40 (1.21-1.61)</td>
</tr>
<tr>
<td>(P homog&lt;0.0001)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Europe and North America, respectively (Table II). This may prove to be a gross underestimate, given recent published prevalence data from Malaysia, Indonesia, and China.

Indonesia is expected to have the greatest absolute increase in adults with T2DM, rising from 3.4 million in 2010 to 16.5 million in 2030. Pramono et al. in a recent epidemiological study conducted in 2007, noted that 4.1% of the total 5.6% of the population found to have diabetes were undiagnosed. In addition, the main predictive factors for diabetes were age, visceral obesity, hypertension, and smoking.

Malaysia is already experiencing an epidemic of diabetes, with 11.6% of the population above the age of 18 years found to have diabetes in the 3rd National Health and Morbidity Survey conducted in 2006. Much of this has been driven by the associated increasing trend in obesity/overweight, of 33.6% and 19.5%, respectively. In the most recently released 4th National Health and Morbidity Survey conducted in 2011, the prevalence of diabetes has jumped to 20% (Ministry of Health Malaysia report, 2012).

For China, in a survey conducted from 2007-2008, the age-standardized prevalence of total diabetes was 9.7%, accounting for 92.4 million adults with diabetes. This number alone is higher than that projected in Shaw’s estimate of 62.6 million in 2030.

Asia is, therefore, the “hotspot” for diabetes and will remain so in the near future. The resultant economic burden of therapy for controlling glycermia as well as management of diabetic complications will be a strain on governmental funds as many of these are developing countries with limited financial resources.

Understanding pathophysiology – Asian T2DM

Recognition of the major underlying pathophysiological processes that determine T2DM occurrence in the Asian individual will help clinicians make appropriate therapeutic decisions.

- Role of β-cell secretory dysfunction

β-Cell secretory dysfunction is thought to play a bigger role in the pathogenesis of T2DM in the Asian population than in whites. In whites, β-cell mass in patients with T2DM has been shown to be reduced by 40%-60% in human autopsy studies. Similar to Butler’s cadaveric study, Yoon et al. reported that β-cell volume was reduced to less than 50% in pancreatectomy specimens of nonobese Korean T2DM subjects, compared with that of BMI-matched normal controls. In this elegant study, β-cell volume correlated significantly with BMI: the clinical implication being that the lower the BMI, the greater the loss in β-cell mass. In addition, α-cell mass was observed to be increased, with a resultant higher α/β ratio than in controls. These findings support the role of selective β-cell loss in the pathogenesis of T2DM.

Clinical observations and experimental data support a close interrelationship between reduction in β-cell mass and β-cell dysfunction. Human donors who underwent a 50% pancreatectomy eventually developed diabetes. Loss of β-cell mass was noted to be associated with increased β-cell apoptosis, while new islet formation rates and β-cell replication were noted to remain normal.

In addition, data from Japanese populations found that impaired early-phase insulin secretion, assessed by the insulinogenic index during the oral glucose tolerance test, was the initial abnormality in the develop-

Table I. Mean values of baseline variables – Asia.

<table>
<thead>
<tr>
<th>Country</th>
<th>No. of adults with diabetes (millions)</th>
<th>No. of adults with diabetes (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>50.8</td>
<td>87.0</td>
</tr>
<tr>
<td>China</td>
<td>43.2</td>
<td>62.6</td>
</tr>
<tr>
<td>USA</td>
<td>26.8</td>
<td>36.0</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>9.6</td>
<td>13.8</td>
</tr>
<tr>
<td>Brazil</td>
<td>7.6</td>
<td>12.7</td>
</tr>
<tr>
<td>Germany</td>
<td>7.5</td>
<td>11.9</td>
</tr>
<tr>
<td>Pakistan</td>
<td>7.1</td>
<td>10.4</td>
</tr>
<tr>
<td>Japan</td>
<td>7.1</td>
<td>10.3</td>
</tr>
<tr>
<td>Indonesia</td>
<td>7.0</td>
<td>8.6</td>
</tr>
<tr>
<td>Mexico</td>
<td>6.8</td>
<td>8.6</td>
</tr>
</tbody>
</table>
ment of glucose intolerance (Figure 2A and B). When progressing from normal glucose tolerance (NGT) to impaired glucose tolerance (IGT), there was a 50% loss of β-cell secretory function. There was a further loss of up to 80% of β-cell function once frank DM ensued. In contrast, when progressing from NGT to IGT and subsequently to DM, insulin resistance increased by only approximately 2-fold. These findings confirmed the earlier study by Matsumoto et al. These data clearly show the clinical relevance and importance of lower basal and impaired early-phase insulin secretion in the pathogenesis of Asian T2DM. Therapeutic agents that address β-cell dysfunction would be expected to play a major role in achieving glycemic control in these individuals.

**Role of insulin resistance**

In general, the Asian T2DM individual has a lower mean BMI (23-25 kg/m²), as shown in Table I. Asian populations have more visceral fat for any given BMI. Deurenberg-Yap et al reviewed this in a multiethnic population in Singapore and concluded that the equivalent BMI cutoff for obesity in Asians is 3 kg/m² less than that for whites, ie, 27 kg/m². In fact, the “metabolically obese” phenotype among individuals of normal weight is a common phenomenon found in Asians, notably Asian Indians. This phenotype, characterized by a higher degree of abdominal obesity despite a normal BMI, a higher proportion of body fat, and increased insulin resistance compared with whites, renders these populations more highly susceptible to development of diabetes. In a study of a group of healthy Asian Indians compared with age- and BMI-matched whites, found that Asian Indians had significantly more total abdominal fat and visceral fat (assessed by computed tomography scan), had typical metabolic dyslipidemia with low levels of high-density lipoprotein cholesterol, had elevated triglycerides, and were profoundly insulin resistant, as assessed by the euglycemic hyperinsulinemic clamp, compared with their white counterparts. Notably, the mean BMI of these healthy Asian Indians was 23 kg/m².

In the UKPDS, 10% of the entire cohort was of Asian Indian origin. These Asian Indian patients were significantly younger, included more men, and had a lower mean BMI than the white and Afro-Caribbean patients (P<0.001). The Asian Indian cohort was the most insulin resistant, as assessed by the euglycemic hyperinsulinemic clamp, compared with their white counterparts.

**Optimizing glucose management of the Asian T2DM subject – choice of therapeutic agent**

It is important to consider the contribution of impaired insulin secretion and insulin resistance to the development of diabetes as these have therapeutic significance. All current guidelines (including those from the International Diabetes Federation in 2011 and those from the American Diabetes Association/European Association for the Study of Diabetes in 2012) continue to include sulfonylureas (SUs) as a possible add-on therapy following failure of metformin monotherapy or as a first-line agent in patients who are intolerant to metformin or where metformin is contraindicated. Metformin will continue to be an important therapeutic agent as the Asian T2DM subject has a greater percentage of visceral fat and lower muscle mass, for any given BMI. Insulin resistance has also been shown to occur at lower BMI levels. Use as first-line is recommended in most guidelines (irrespective of BMI), including those from many Asian countries.
However, in many Asian T2DM subjects, SUs would be an appropriate choice of therapeutic agent, as they address the major β-cell secretory dysfunction. When deciding which SU to choose, consideration of the individual drugs’ pharmacokinetics and pharmacodynamics would aid in decision making. The differences in metabolism of the various SUs are likely to affect their efficacy. Cytochrome P450 (CYP) 2C9 and CYP2C19 are responsible for the metabolism of over 20% of clinical therapeutic drugs. CYP2C9 genetic polymorphism is known to be responsible for the metabolism of oral SUs, eg, glibenclamide and glimepiride. The metabolites of both glibenclamide and glimepiride are metabolically active and have persistent hypoglycemic potential.

In contrast, CYP2C19 genetic polymorphism appears to play an important role in the pharmacokinetics of gliclazide modified release (MR). For example, the area under the curve for gliclazide is significantly higher by 3.4-fold (95% confidence interval [CI], 2.5-4.7; P<0.01) in CYP2C19 poor metabolizer (PM) subjects compared with subjects with other genetic polymorphisms.35 The half-life (t1/2) is also prolonged from 15.1 to 44.5 h (P<0.01). Similar increases in serum levels of gliclazide were found in the multiple-dose study.

In addition, there is a greater prevalence (20%) of CYP2C19 PMs in Asian populations than in whites and Africans (5%). This can account for the greater antihyperglycemic response to gliclazide therapy in some Asian diabetic subjects. This will also explain the greater variability of response to gliclazide MR therapy in Asian subjects.

Lessons from ADVANCE
Lessons learned from the mega outcome trial, the ADVANCE study (Action in Diabetes and Vascular disease: PreterAx and Dia-microN MR Controlled Evaluation), are relevant for the Asian T2DM individual. This is because approximately 40% of the ADVANCE study subjects were from Asia, namely from China, India, Malaysia, and the Philippines.

ADVANCE used gliclazide MR as the active therapeutic agent in the intensive arm. Subjects randomized to the standard arm were allowed to be treated with other SUs. The objective was to achieve glycemic control with an HbA1c target of 6.5% in the intensive arm. This was successfully achieved, and it is important to note that it was achieved without weight increase and with only a low risk of severe hypoglycemia.36 Of the 91% on gliclazide MR in the intensive arm, 70% were taking gliclazide MR 120 mg daily, with 74% on metformin, 17% on thiazolidinediones, 19% on acarbose, and 40% on insulin.

Results reported by Clarke et al37 (2010) show that Asian T2DM subjects in the ADVANCE study suffer from significantly more cerebrovascular events and nephropathy events compared with other ethnic groups (Figure 3).37

Increased risk of renal disease and a requirement for renal replacement therapy have been previously noted as particular problems in Asian diabetic subjects. Karter et al,38 in the longitudinal observational study in the Kaiser Permanente Medical Care Program from 1995-1998, noted that there are clear...
ethnic disparities in diabetic complications, with Asian, Latino, and black diabetic subjects having higher levels of end-stage renal disease than their white counterparts (Figure 4A).38

Yoon et al6 also noted that diabetes was the primary cause behind the large proportion of patients with end-stage renal disease on dialysis in many Asian countries, including Malaysia, Korea, Pakistan, Taiwan, and the Philippines (Figure 4B).7 These data confirm the global trend of diabetes as the main cause of end-stage renal failure requiring renal replacement therapy. Therefore, given the higher predilection for developing renal complications noted in Asian T2DM subjects, the improved renal outcomes found in the ADVANCE study take on greater significance.

In ADVANCE, achievement of the HbA1c target of 6.5% provided microvascular benefits, specifically, a 21% reduction in renal events (P=0.006), 9% reduction in microalbuminuria (P=0.018), and 30% reduction in macroalbuminuria (P<0.001) (Figure 5).36 Improvement in the urinary albumin-creatinine ratio observed at the end of the ADVANCE study was found to correlate with lower risk of cardiovascular death.39 In the context of the Asian T2DM subject, the prevention of albuminuria progression and subsequent renal failure would be expected to translate to lower morbidity and hopefully, eventual reduction in cardiovascular mortality.

ADVANCE-ON (the ADVANCE posttrial Observational study), the observational follow-up phase of ADVANCE is currently ongoing and is expected to provide further important answers about potential cardiovascular benefits after successful glucose control.

Conclusion
The Asian T2DM patient will dominate the diabetes landscape in the foreseeable future, with epidemic proportions of people with diabetes onset at a younger age, with the “metabolically obese” phenotype. With the expectation of increased life expectancy, it is evident that Asian T2DM patients will be exposed to a higher burden of diabetes complications, including renal, cardiovascular, and neurological complications.
spans as a result of improved health care, these people will live longer with the disease. Diabetic complications, both microvascular and macrovascular, have been observed in the Asian diabetic to a similar extent to that reported in whites. Unfortunately, cerebrovascular and renal complications have been noted more frequently in Asians. The societal costs of managing these will place a burden on the individual. In addition, the potential adverse economic impact will likely overwhelm most governmental budgets.

Affordable therapeutic agents with proven efficacy and outcome studies to back their utility will be the important factors determining how clinicians make appropriate decisions in the challenging task of choosing antihyperglycemic agents. Recent updates on glycemic goals do not back down from our management strategy—which was always to individualize targets—but rather reaffirm it. The lower the better should still be the goal, the only precaution being that this should be done without causing hypoglycemia.

Keywords: ADVANCE; Asian diabetes; body mass index; insulin secretory dysfunction; renal complications; type 2 diabetes mellitus

References
FAUT-IL UNE PRISE EN CHARGE BASÉE SUR DES PREUVES POUR TOUS LES GROUPES ETHNIQUES DE DIABÉTIQUES ?

L’Asie est le “point chaud” du diabète de type 2 (DT2), toutes les études épidémiologiques récentes y montrant en effet une augmentation rapide de sa prévalence dans un délai plus court que pour d’autres régions, la Chine et l’Inde ayant le plus grand nombre de diabétiques. Outre le grand nombre de personnes qu’il touche, le diabète survient en Asie chez des individus plus jeunes et dont l’indice de masse corporelle est plus bas (on parle de phénotype d’obésité métabolique). Le diabète débutant plus précocement, sa durée est donc plus longue, ce qui entraîne un risque plus élevé de développer des complications. Comprendre quelles anomalies physiopathologiques clés jouent un rôle majeur dans le déclenchement du DT2 aidera les médecins à choisir les traitements appropriés. Le rôle important de la perte de la masse des cellules β et le dysfonctionnement de leur sécrétion chez le patient asiatique diabétique justifie le choix de l’utilisation des sulfonylurées (SU), soit après l’échec d’une monothérapie à la metformine, soit comme traitement de première intention chez les patients intolérants à la metformine ou pour qui la metformine est contre-indiquée. Les recommandations les plus récentes (International Diabetes Federation 2011 et American Diabetes Association/European Association for the Study of diabetes 2012) pour la prise en charge du diabète et de l’hyperglycémie ont encore renforcé l’importance des SU. Les résultats obtenus avec le gliclazide LM dans l’étude ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR evaluation) ont montré son utilité clinique. L’étude ADVANCE comprenant une cohorte asiatique importante, ses résultats et ses enseignements peuvent donc s’appliquer directement au patient asiatique atteint de DT2.
Though insulin resistance and β-cell failure are hallmarks of type 2 diabetes mellitus, the course and treatment of the disease may also be influenced by local and environmental factors. Indeed, there is a growing body of evidence showing that ethnicity may influence diagnosis, the incidence of microvascular and macrovascular complications, the type, and even the response to different medications. Along with ethnicity, socioeconomic status also seems to be an important determinant of diabetic complications. Although these differences have been demonstrated in minorities and subpopulations in the United States, Asia, and Europe, data from South America is scarce. Unfortunately, there is no scientific evidence of good quality comparing data from South America with these communities or even comparing data from different South American populations. Until this information is available, it will remain impossible to define a specific guideline for diabetes treatment in this particular population. In the meantime, local South American diabetes societies should develop guidelines based on the American Diabetes Association and European Association for the Study of Diabetes statements, considering specific characteristics of each country.

Type 2 diabetes mellitus (DM) prevalence is increasing worldwide. In 2011, Danaei et al.1 published a very interesting systematic analysis including 370 country-years and 2.7 million participants from health examination surveys and epidemiological studies. Age-standardized prevalence of diabetes was 9.8% (8.6-11.2) in men and 9.2% (8.0-10.5) in women in 2008, leading to an estimated 173 (151-197) million men and 173 (151-197) million women with diabetes. Of those with diabetes, 40% (about 138 million) were from China and India, 10% (about 36 million) from the United States and Russia, and 12% (about 42 million) from Brazil, Pakistan, Indonesia, Japan, and Mexico. In 1980, age-standardized prevalence was 8.3% (6.5-10.4) in adult men and 7.5% (5.8-9.6) in women, yielding 77 (60-97) million men and 76 (58-97) million women with diabetes. Unfortunately, specific data from South America were very scarce. For instance, only one study was included in this analysis from Uruguay, Paraguay, Venezuela, and Argentina. Peru and Colombia contributed with 3 studies, Chile with 2 studies, and Brazil with 6 studies. These results confirmed how little is currently known and how little scientific information is available about type 2 DM in South America.
Also in 2011, the document entitled “Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)” was published, replacing the previous ADA/EASD statement from 2008 (“Medical management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy”). Despite substantial differences in both documents, the purpose of these two manuscripts was to review the available information on the benefits and risks of glycemic control as well as evidence concerning efficacy and safety of several drug classes used to treat type 2 DM. Review of the medical literature led to the development of specific recommendations for type 2 DM treatment.

The published consensus and/or guidelines by the ADA/EASD is often seen as the official recommendation for diabetes treatment worldwide. However, no specific information was included in those documents regarding an approach to management of type 2 DM in specific populations, particularly South American and African populations. Therefore, one should ask: Do these recommendations also apply to the South American population? Is there enough evidence to suggest that the course or the treatment of type 2 DM should be different in these populations?

**Does ethnicity modulate the development of insulin resistance?**

Type 2 DM is a disease characterized by insulin resistance (IR) and progressive \(\beta\)-cell failure. IR is defined as an inadequate response by insulin target tissues, such as skeletal muscle, liver, and adipose tissue, to the physiological effects of circulating insulin. Ethnicity seems to be one of the IR determinants in specific populations. For instance, higher degrees of IR were seen among African Americans and Latinos in comparison with whites. Studies that compared various populations of West African descendants (including African Americans and native Ghanaians) and whites have reported higher degrees of IR among West African descendants. Interestingly, it seems that alterations in hepatic insulin clearance in African populations may partially explain these findings. These studies provide evidence for genetically driven IR as an underlying factor for the ethnic disparities in the prevalence of type 2 DM. Unfortunately, there are no studies comparing South American populations with any other populations worldwide or even within South America.

**Does ethnicity influence the development of type 2 DM?**

The role of ethnicity in DM development was contested after some results presented by the Diabetes Prevention Program (DPP). The incidence of type 2 DM was found to be similar (−1%) among African Americans, Asian Americans and Pacific Islanders, white Americans, Hispanic Americans, and Native Americans. The well-known ethnic disparity in the risk of type 2 DM was surprisingly not evident among the DPP cohort with impaired glucose tolerance (IGT), which was followed for up to four years. The finding of similar transethnic diabetes rates in the DPP suggests that once individuals have progressed from normal glucose tolerance to IGT, the risk of further progression to diabetes is the same across ethnic groups. Thus, it seems that ethnicity and genetic factors may play a role in the progression from a normal to impaired fasting glucose (IFG) state, but not from IFG to type 2 DM.

**Does ethnicity have an impact on the development of diabetes complications?**

There is evidence suggesting that ethnicity may be one of the factors related to the development of diabetic complications. However, once again, most of the studies evaluate different populations in the United States and Europe and their results might not be relevant to South America. For instance, the prevalence of diabetic retinopathy in diabetic individuals was 46% higher in African Americans and 84% higher in Mexican Americans compared with non-Hispanic whites. African Americans and Mexican Americans also had higher rates of moderate and severe retinopathy and higher levels of many putative risk factors for retinopathy. Similarly, the rates of end-stage renal disease (ESRD) are approximately threefold or higher in African Americans, Latinos, and Native Americans compared with whites. The rates of hospitalization for lower extremity ulcers are similar across all ethnic groups, but lower extremity amputation (LEA) rates are two to three times higher in Mexican American and African American patients compared with whites. According to Samuel Dagogo-Jack, these rather large effects of glycemic control on target organ end points indicate that genetic factors are permissive rather than obligate determinants of risk.

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**SELECTED ABBREVIATIONS AND ACRONYMS**

- ADA: American Diabetes Association
- ALAD: Asociación Latinoamericana de Diabetes
- CHF: congestive heart failure
- DM: diabetes mellitus
- DPP: Diabetes Prevention Program
- EASD: European Association for the Study of Diabetes
- ESRD: end-stage renal disease
- HbA1c: glycated hemoglobin
- IFG: impaired fasting glucose
- IGT: impaired glucose tolerance
- IR: insulin resistance
- LEA: lower extremity amputation
- MI: myocardial infarction
- NHANES: National Health And Nutrition Examination Survey
- PHS: public health system
- SMBG: self-monitoring of blood glucose
The impact of ethnicity on diabetic complications was also demonstrated by the Kaiser Permanente Medical Care Program. Karter et al reported that despite comparable health insurance coverage, ethnic disparities persisted for myocardial infarction (MI), stroke, congestive heart failure (CHF), ESRD, and LEA. Interestingly, patterns of ethnic differences were not consistent across complications and persisted even after adjustment for demographic and socioeconomic factors. For instance, minority populations (Asians and Latinos) had lower incidence of MI, stroke, and CHF. On the other hand, they had a higher incidence of ESRD. The authors concluded that the persistence of ethnic disparities after adjustment suggests a possible genetic origin, the contribution of unmeasured environmental factors, or a combination of these factors. It remains to be determined if the disparities would also be found in the South American population and what impact the environment would have on diabetic complications in a continent characterized by great discrepancies among their countries and populations.

These results have also been contested by other studies. For instance, after adjustment for a well-known risk factor for retinopathy in the NHANES (National Health And Nutrition Examination Survey) III, the black/white disparity was no longer significant.

**Does socioeconomic status affect the development of DM and its complications?**

Although significantly different with regard to ethnicity, African American, Latino, and Mexican American populations share a determinant characteristic with South American populations: low socioeconomic status. There is compelling evidence that low socioeconomic status, limitations in access to care, lack of health insurance or underinsurance, and other socioeconomic barriers, all common in South American countries, are important contributors to the increased burden of diabetes and its complications.

In line with these findings, there are results showing that in African American populations, the development of diabetes ketoacidosis has been directly related to the cessation of insulin.

The most important challenge in determining the particular effect of ethnicity on diabetic complications is how to separate ethnicity from socioeconomic status. A study by Karter et al highlights the relevance in making this distinction. Throughout their study, the authors demonstrated that the marked ethnic disparity in LEA rates observed in the general diabetic population is not evident in an ethnically diverse population with uniform health care coverage. Even the low frequency of self-monitoring of blood glucose (SMBG) has socioeconomic underpinnings: with identical health insurance coverage, the frequency of SMBG among African Americans increased to match or exceed that of Asian, Latino, or white patients.

**How does socioeconomic status influence DM treatment in South America?**

Cost is one factor that must be taken into account when defining a specific treatment for type 2 DM in a specific population. The choice of medications supported by guidelines may be based mainly on efficacy and safety, but this becomes secondary when defining guidelines for South America and Africa. In most countries in Europe and the United States, the government provides either part or all of the treatment for most chronic diseases, whatever medication is used. In South America, there are a limited number of medications available in the public health system (PHS).

For the majority of type 2 DM patients, treatment will be chosen according to the medications available in the PHS. In most South American countries, only metformin and sulfonylureas (mostly chlorpropamide and glibenclamide) are available. For patients who do not tolerate these medications, options are limited to regular insulin and neutral protamine Hagedorn (NPH) insulin. Pioglitazone, dipeptidyl peptidase 4 inhibitors, liRaglutide, exenatide, and insulin analogues are available for only a small part of the population who can afford the high costs of these therapies. Importantly, neither the government nor private health insurance reimburse these medications. As a consequence, the development of a specific guideline for our region needs to consider this aspect since it is the major determinant of the kind of treatment most of the population will have access to.

In some countries, or more specifically, in some regions of certain countries, some additional medications may also be available. As an example, there are some regions in Brazil where pioglitazone, dipeptidyl peptidase 4 inhibitors, liraglutide, exenatide, and insulin analogues can be provided to a limited number of type 1 and type 2 DM patients.

The impact of socioeconomic status on glycemic control, however, is still controversial. An analysis of the NHANES III data by Harris et al demonstrated that education, income, health insurance coverage, number of physician visits per year, and other variables were not predictive of poor glycemic control in a sample of non-Hispanic whites, non-Hispanic blacks, and Mexican Americans. On the other hand, race/ethnicity was associated with differences in diabetes treatment. A larger proportion of non-Hispanic black men and women were treated with insulin compared with non-Hispanic whites and Mexican Americans.

This finding was complemented by a smaller proportion of non-Hispanic blacks using oral agents, such that the proportions that were treated pharmacologically were similar for each racial or ethnic group. Finally, for those treated with insulin, a higher proportion of non-Hispanic whites used multiple insulin injections compared with non-Hispanic blacks and Mexican Americans.
The impact of ethnicity on the type of diabetes medication used has also been recently demonstrated in the UK population.\textsuperscript{18} White patients were less likely to be on intensive diabetes treatment (either “combined oral” or “insulin”) than were South Asian and black African/Caribbean patients, but South Asians were less likely to be on insulin than were whites. Interestingly, glycated hemoglobin (HbA\textsubscript{1c}) control to 7.5% or less was worse in South Asian and black African/Caribbean patients than in whites despite more intensive treatment in these ethnic groups. In this study, James et al suggested that both socioeconomic status and ethnicity are independently associated with glycemic control.

The lack of association of glycemic control with socioeconomic status was also found in a Michigan community study of whites\textsuperscript{19} and a South Carolina study of blacks and whites\textsuperscript{20} in which poor glycemic control was not associated with educational level. These studies reflect the impact of socioeconomic status and ethnicity in the United States and the United Kingdom. Do these results also apply to South America? How would differences in the PHS affect these findings? What would be the most important factor related to diabetes treatment in South America: socioeconomic status or ethnicity?

\textbf{Should DM treatment in South America be different?}

In times of evidence-based medicine and globalization, the development of a specific guideline for South America will only be possible if specific, well-designed controlled trials are available. Unfortunately, this is not the reality. However, it is worth mentioning that most of the large clinical trials currently being carried out have research centers in South America. Therefore, these studies are expected to reflect, partially, the responses to different therapies in the South American population. At this very moment, there is no study that indicates, or even suggests, that the population of South America would respond differently from other populations, even with some of the differences previously mentioned above.

\textbf{Does South America need a different guideline for the diagnosis and treatment of DM?}

Despite the fact that South American populations have characteristics that are completely different from those in Europe and the United States, there are certain aspects that must be taken into consideration when developing specific guidelines for the diagnosis of DM in South America.

\begin{itemize}
  \item There are no long-term studies evaluating the course of diabetes in South America. There is no evidence indicating that the incidence of diabetic complications would be significantly influenced by ethnicity in South American populations.
  \item There are no specific studies comparing the differences among South American countries with regard to DM or IFG diagnoses. A recent analysis of the ORIGIN (Outcome Reduction with Initial Glargine Intervention) study has shown that the strong correlation found between HbA\textsubscript{1c} and fasting glucose is affected neither by ethnic nor by geographical factors.\textsuperscript{21} The strength of the study was the large number of subjects available for the overall and subgroup analyses. These observations were limited by the fact that glucose and HbA\textsubscript{1c} values were measured locally using a variety of assays worldwide, and that a mathematical approach was used to adjust for differences in each laboratory’s normal range for HbA\textsubscript{1c}. Thus, laboratory-related variability may have influenced the results. Also, information on the presence of variant hemoglobins or other physiological factors that might affect HbA\textsubscript{1c} values was not available, and whether such factors may have altered the FPG-HbA\textsubscript{1c} relationships observed is unknown.
\end{itemize}

\textbf{What is the position of the Asociación Latinoamericana de Diabetes?}

There are many societies and associations for the study of diabetes in South America (Table I). Generally, these societies are responsible for establishing local guidelines for type 2 DM treatment according to specific characteristics of the country. Some of them are affiliated or somehow associated with the local endocrinology societies. Most of the current guidelines for South American countries closely follow the ADA and EASD recommendations with slight differences. All South American diabetes associations are affiliated with the Asociación Latinoamericana de Diabetes (ALAD). In 2010, with the approval

\begin{table}[h!]
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\begin{tabular}{|l|}
\hline
Sociedad Argentina de Diabetes & www.diabetes.org.ar \\
Sociedad Boliviana de Endocrinología, Metabolismo y Nutrición & www.galenored.com/sbemn1/ \\
Sociedad Brasileira de Diabetes & www.diabetes.org.br \\
Sociedad Chilena de Endocrinología y Diabetes & www.soched.cl \\
Federación Diabetológica Colombiana & www.fdc.org.co \\
Sociedad Ecuatoriana de Endocrinología y Metabolismo & \\
Sociedad Peruana de Endocrinología & www.endocrinoperu.org \\
Sociedad de Diabetes y Nutrición del Uruguay & www.diabetologia.org.uy \\
Federación Nacional de Asociaciones y Unidades de Diabetes de Venezuela & www.fenadiabetes.org.ve \\
\hline
\end{tabular}
\caption{Diabetes societies and associations in South America.}
\end{table}
of all the South American diabetes societies, the ALAD published a guideline\(^2\) in an attempt to standardize diabetes treatment in Latin America. Although many of the recommendations are similar to the American and European ones, some specific points are worth mentioning:

- **Metformin is the first option for all type 2 DM patients.**
- If a second medication is needed, options to be considered are sulfonylureas, pioglitazone, acarbose, dipeptidyl peptidase 4 inhibitors, and glucagon-like peptide-1 (GLP-1) analogues. One should note that despite being published in 2010, this guideline sustains that there is no obligatory second medication, and that treatment should be individualized according to the patient profile. Another point that needs mentioning is that the metformin/sulfonylurea combination is the most commonly prescribed treatment for DM in Latin America. The obvious explanation is its lower cost.
- **The SMBG should be carried out according to each patient’s need.** Self-monitoring has become more accessible in South America, though cost is still a barrier. In some countries (such as Brazil), there are specific protocols for providing glucose meters to patients, with a varied quantity of test strips, in accordance with the DM classification and medication prescribed.
- The document claims that there is an insufficient number of specialists for DM treatment in Latin America. Therefore, general practitioners should be capable of carrying out the initial treatment and then, if treatment goals are not achieved in 3 to 6 months, the patient must be referred to a specialist.
- The document also provides general information for the prescription of diet and physical activity for the diabetic patient.

It is important to point out that references used in the development of this document were the same as those used for the ADA and EASD guidelines. Thus, though considering this to be a specific document for a specific population, it is not based on specific studies within the South American population.

**Conclusion**

Ethnicity seems to be a relevant risk factor for diabetes and its complications. Unfortunately, there is no scientific evidence of good quality comparing data from South American populations with that from other countries or even comparing data from different populations within South America. Until such information becomes available, making it possible to define specific guidelines for diabetes treatment in this population, local South American diabetes societies should develop guidelines based on the ADA and EASD statements, considering specific characteristics of each country. Defining a global strategy for diabetes diagnosis and management should be seen as an effort to unite specific populations to fight a devastating disease.

References


Keywords: ADA; Associación Latinoamericana de Diabetes; EASD; ethnicity; guidelines; socioeconomic status; type 2 diabetes mellitus; South America
The importance of diabetes education in the management of patients, including the importance of monitoring, self-management approaches, and the skills of nurse practitioners has long been recognized by clinicians. Modern approaches in diabetes education must focus on multiple perspectives such as reducing complication rates and hospital admissions, but also on enhancing quality of life and well-being. While both individual (one-on-one) and group educational approaches have been studied in the context of type 1 and type 2 diabetes management, more consistent benefits have been observed in type 1 diabetes subjects. Diabetes education for patients (and carers) in a group setting seems to have added advantages, but reinforcement and repeat teaching sessions are needed for longer-lasting effects. More well-designed studies in this area are needed.

Historically, pioneers of diabetes education included Dr Roma in Portugal a century ago, R. D. Lawrence in the United Kingdom, Joslin and Miller in the United States, and Assal in Switzerland. More recently, significant work in diabetes education, including some attention to psychological influences, has been provided by individuals such as Bradley, Anderson, Day, and Fox. These early developments recognized the importance of monitoring, self-management approaches, utility of nurse practitioners, and even 24-h telephone support. With this came the job specifications for diabetes nurse educators and specialist nurses. A stimulus for this drive was the view held by clinicians that diabetes self-care was a paramount objective to be achieved if hospital admission rates were to be tackled, if hypoglycemic and ketoacidotic episodes were to be avoided, and if early blindness was to be prevented. Indeed, any one of these events occurring was a marker of educational failure! It has even been suggested that educational methods may have played key roles in some of the outcome gains seen in the landmark intervention studies of the DCCT (Diabetes Control and Complications Trial) and the UKPDS (United Kingdom Prospective Diabetes Study).

Modern-day approaches employ various learning models and methods, adult educational theory, life-long learning, behavioral modification, a better understanding of the psychological state of a patient, aligning educational initiatives with medical treatment, involvement of the family and carers, more insightful use of information technology to attain goals of care, and simulated medical education. In the United Kingdom, we have seen the emergence of two robust methods of diabetes educa-
tional learning. The first is DAFNE (Dose Adjustment For Normal Eating) which is a group program for adults with type 1 diabetes. DAFNE is based on regular glucose testing before meals and at bedtime, use of rapid-acting insulin with meals containing carbohydrates, and maintaining “background” insulin (long-acting insulin) levels each day (http://www.dafne.uk.com/). The second method has been designed to assist those with type 2 diabetes and is called the DESMOND program (Diabetes Education and Self-Management for Ongoing and Newly Diagnosed). It was developed within the UK National Health Service (NHS) (http://www.desmonddiabetes.org.uk). Much of these newer methods are embraced within the ethos of structured patient education in diabetes which is supposed to be person-centered, theory-driven, evidence-based, and resource-effective. It is meant to be delivered by educators (usually multidisciplinary) who have received appropriate training and have the appropriate skill set and competencies to provide a program that meets the learning objectives of a wide range of patients and their carers.

It is thus accepted that diabetes education for patients (and probably carers) is an integral part of diabetes management and must be a consistent and ongoing process; it should be adapted to differing learning styles of patients, and allow a normal lifestyle as possible. Other key essential requirements include evaluating the learning needs of participants, varying teaching methods as necessary, and providing the choice of individual or group sessions. In this article, we shall examine some of the key generic aspects of diabetes education and how these may be seen as part of educational programs designed for the individual and for participants organized in groups. My focus is predominantly on type 2 diabetes mellitus, although many of these generic features apply to both type 1 and type 2 diabetes.

**Primary goals of a diabetes education program**
The primary goals of a diabetes education program directed towards people with diabetes are outlined in Box 1:

<table>
<thead>
<tr>
<th>Box 1</th>
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<tbody>
<tr>
<td>– Help them to accept their condition.</td>
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<tr>
<td>– Integrate the key aspects of diabetes self-management into their daily lifestyle.</td>
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<tr>
<td>– Enhance their knowledge of diabetes to have better insight into the importance of metabolic control.</td>
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<tr>
<td>– Equip them to have the skills and motivation to deal with diabetes-related problems when they arise.</td>
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**Developing the learning environment**
Several factors might have relevance in ensuring that the most optimal learning environment is present. It is mostly accepted that the learning program should be conducted where patients are most comfortable and, when possible, educators should use a problem-based learning approach. Thus, the program can be carried out in a patient’s home, in a local diabetes center, or in a general practitioner’s office. In Box 2 are listed 3 key factors which assist the learning strategy:

<table>
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<th>Box 2</th>
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<tr>
<td>– Comfortable seating, good lighting, uncluttered space, and no distractions.</td>
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<tr>
<td>– Well-planned sessions that avoid conflict with transport issues, meals, insulin administration times, or other clinical appointments.</td>
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<tr>
<td>– Quickly established learning culture; avoidance of too much emphasis on one area such as glucose control.</td>
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**Importance of behavioral change**
Unless people with diabetes change their behavior to modify their lifestyle, attain control of their metabolic state, and learn the practical skills of diabetes self-care, the process of diabetes education will have failed. Some factors that have been identified that might influence behavioral change are shown in Box 3 and are based on the model of Ajzen and Fishbein (1980).  

<table>
<thead>
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<th>Box 3</th>
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<tr>
<td>– Level of basic diabetes knowledge at baseline.</td>
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<td>– Attitudinal behavior and level of intention to “change.”</td>
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<tr>
<td>– Social context and current lifestyle choice.</td>
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<td>– Demographic profile.</td>
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<tr>
<td>– Perception by the patient of the existence of “barriers” that reduce the likelihood of the process being effective.</td>
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<tr>
<td>– Perception by the patient on whether the program is actually “working.”</td>
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</table>

Other theories of behavior change, such as social cognitive theory by Bandura, 4 have been invoked to explain individual behavior and structure interventions. The concept of “self-efficacy” has been used as a template to explain why personal behavior toward achieving goals can be affected so markedly by other influences, such as prior history of tackling the same or similar problems, outside persuading influences which could be emotional or work related, for example, and by the psychological state of the individual. Skinner, a behavioral psychologist, concluded that complex behavior change (as may be expected in self-managing diabetes) can only be realized if it results from a series of positive changes to smaller domains with simpler changes required, and that this process was likely to be more successful if individuals duplicated successful behaviors of others and these processes were reinforced. 1 It should also be remembered that other behavioral programs may need to be activated to see the full benefits of the diabetes educational strategy (structured education), such as guidance relevant to physical activity, smoking cessation, and obesity.
Special characteristics of older patients and their learning styles

From a number of important standpoints, older people with diabetes present major, often unique challenges to diabetes educational programs. These may be associated with age-related changes in sensory perceptions (vision, hearing), demographics, or short-term memory decline, and information processing times. Accompanying these may be changes in motor skills, social and family dynamics, and the level of medical comorbidities and functional loss.

Encouraging older people to take an active part in diabetes educational programs has not received the same focus of attention among health professionals who justly say that their attentions are mainly devoted to younger type 1 and type 2 subjects. Ensuring that safe and easy access is available to learning areas, emphasizing the importance of empowerment, involving family and carers, and asking for a level of active participation that utilizes to the maximum the cognitive and intellectual level of the patient are ways that increase the success rate of the educational process. Work in this area recently showed that a tailored telehealth program of diabetes education in older Hispanic American and African American subjects led to better adherence to therapy and improved glycated hemoglobin (HbA1c).7

Evidence for effective diabetes education

The benefit of diabetes educational intervention is not as clear cut as you may imagine. Indeed, for many years, the literature reported both successes and failures! Many studies focused on outcomes that could be measured relatively easily, such as level of glycemic control or blood pressure reduction. However, key components of diabetes self-care, such as reduction in severe hypoglycemia rate, reductions in hospitalization for foot care problems, and adherence rates to therapy were often ignored and methods used to assess/evaluate these were superficial or inaccurate or inappropriate. Varying methodological issues, duration of the intervention, quality and expertise of the educators were other factors that were not put into the “effectiveness” equation.

A systematic review of the clinical- and cost-effectiveness of patient educational models in both type 1 and type 2 diabetes9 was used as a basis of developing guidance in the United Kingdom in diabetes education. This review identified 24 studies (18 randomized controlled trials and 6 clinically controlled trials) in which the study design, methodology, and quality of reporting was relatively low. Only 2 studies reported cost-effectiveness outcomes. The results of the review are summarized as follows (Box 4):

Box 4

Type 1 diabetes – Education programs offered as part of a package of care involving intensified treatment interventions are associated with significant and long-lasting improvements in metabolic control and reductions in complications. The DAFNE program, which consists of 5 days of intensive structured training delivered to groups of 6-8 patients was undergoing further evaluation at the time of the review.

Type 2 diabetes – No consistent benefits observed.

Studies in both types of diabetes, it was not possible to identify what main elements of the interventions used achieved positive results. Many of the studies were carried out 5-10 years before the review and outcomes were assessed 12-24 months after baseline assessment. Patient knowledge seemed to be influenced the most in several studies. Most of these interventions were by the group method and those studies that reported benefits usually had a group design.

Cost effectiveness – Not possible to arrive at a conclusion due to scarcity of studies and poor data.

It was quite clear from this review, completed in 2002, that there was not enough evidence for type 2 diabetes and that more research was needed. In 2008, the authors provided an update of their first review.11 They concluded that education delivered by a team of educators, with some degree of reinforcement, may provide the best opportunity for improvements in patient outcomes.

Studies in type 1 diabetes since then have revealed several new insights. For example, this year, a published study of DAFNE in type 1 diabetes demonstrated that over a 12-month period, a structured education program delivered in routine clinical practice not only improves HbA1c while reducing the severe hypoglycemia rate and restoring hypoglycemia awareness, but also reduces psychological distress and improves perceived well-being.10

In type 2 diabetes, a meta-regression analysis,11 which looked at the benefits of quality improvement strategies on glycemic control in type 2 diabetes, demonstrated small to modest improvements in glycemic control. Interestingly, team changes and case management showed more robust improvements, especially for interventions in which case managers could adjust medications without awaiting physician approval. In an-
other study, a telephone peer-delivered intervention study measured the effectiveness of the intervention to enhance self-efficacy in type 2 diabetes and its impact on clinical outcome.\textsuperscript{12} Unfortunately, at 6 months there were no statistically significant differences in self-efficacy scores, HbA\textsubscript{1c}, or other secondary outcome measures. Similarly, in a recently published study, no effect of motivational interviewing on metabolic status or on adherence to medication in people with screen-detected type 2 diabetes was observed.\textsuperscript{13}

A study published in 2008 assessed the effect of a structured, empowerment-based educational system (LAY or “Look After Yourself”) for patients with type 2 diabetes.\textsuperscript{14} The educational program was associated with early benefits in HbA\textsubscript{1c} levels, illness attitudes, and perceived treatment effectiveness; however, at 12 months, only illness attitudes (\textit{P}=0.01), and self-monitoring (\textit{P}=0.002) showed benefit. This was associated with only limited benefits in glucose control.

A recent Cochrane review\textsuperscript{15} of individual patient education for people with type 2 diabetes suggested a benefit of individual education on glycemic control when compared with usual care in a subgroup of those with a baseline HbA\textsubscript{1c} greater than 8%. The review did not demonstrate a significant difference between individual education and usual care. In the small number of studies comparing group and individual education, there appeared to be an equal influence on HbA\textsubscript{1c} at 12 to 18 months.

What to choose – individual or group education for your patient?

Often, the answer to this question will be determined by the patient and/or family, the professional preference of the physician, the quality of staff available to engage in teaching of the course, and available health resources.

A problem-based, frequent, one-on-one consultation is a more appropriate. Diabetes education – key principles of individual or group participation – Sinclair

Conclusion

Patient education models for diabetes still require greater innovation in order to meet the increasing demands of a population of people who are more informed and have higher expectations. Translating what we have learned thus far into effective outcomes needs to become a more consistent process, and back-translation of reactions and responses to learning to inform new research is also required.

Diabetes is a long-term condition that lends itself to a variety of care processes, some centered around chronic disease management, some around a patient-empowerment model, and some around behavioral modification. Diabetes educators need to consider all these approaches in their teaching styles, recognizing always that diabetes is often a complex illness paradigm where a multifaceted intervention may be more appropriate.

Linking diabetes education to patient-centered outcomes can be developed further with the use of, say, telehealth approaches, e-learning and other Web-based methods, but a strong emphasis on patient satisfaction, quality of life, maintaining functional status, and well-being is of paramount importance.

References

3. UK Prospective Study of Therapies of Maturity Onset Diabetes 1: Effect of diet, sulphonylurea, insulin or biguanide therapy on fasting glucose and body weight over one year. Diabetologia. 1983;24:404-411.


Keywords: behavioral change; diabetes education; learning; knowledge; type 1; type 2

L’ÉDUCATION AU DIABÈTE : LES PRINCIPES CLÉS DE LA PARTICIPATION INDIVIDUELLE OU DE GROUPE

Les médecins reconnaissent depuis longtemps l’importance d’une formation spécifique à la prise en charge du diabète, et notamment l’importance de la surveillance, de la prise en charge autonome et des compétences des infirmières. Les techniques modernes de formation sur le diabète doivent se concentrer sur de multiples aspects tels que la réduction des taux de complications et d’admission à l’hôpital, mais aussi mettre l’accent sur la qualité de vie et le bien-être. Les approches pédagogiques de groupe et individualisées ont été étudiées dans le contexte de la prise en charge des diabètes de type 1 et 2, et les bienfaits les plus significatifs ont été observés chez les diabétiques de type 1. Les formations à la prise en charge du diabète dispensées en groupe semblent apporter des bénéfices pour les patients (et les soignants) mais il faut que cet enseignement soit renforcé et répété afin de générer des effets à long terme. Dans ce domaine il est indispensable de mener des études supplémentaires bien conçues.
Evidence from several recent large, randomized, controlled trials suggests that improved glycemic control is associated with a reduced risk for cardiovascular disease (CVD), but that this benefit may be greater in individuals with a shorter duration of diabetes and with no prior history of CVD. Although an as yet unexplained increase in mortality was observed in the ACCORD (Action to Control CardioVascular Risk in Diabetes) trial, this was not seen in the other studies. There is still no definitive evidence that any specific antihyperglycemic agent is associated with CV benefit, although there has been a suggested benefit attributed to metformin in the UKPDS (United Kingdom Prospective Diabetes Study), gliclazide-based therapy in ADVANCE (Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation), and pioglitazone in PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events). As a result of new Federal Drug Administration regulations, a large number of ongoing studies will provide us much additional information on specific agents. These trials will certainly provide important 3- to 5-year safety data on new agents, but may or may not show benefits of specific agents to reduce CV risk. Furthermore, any difference in benefits seen with the various agents may be related not to inherent differences among the drugs, but rather to the study design or to the population studied.

There is a considerable amount of evidence demonstrating that people with diabetes have an increased risk for cardiovascular disease (CVD), that it occurs at an earlier age, and that it is associated with worse outcome. What remains less certain is whether improved glycemic control can reduce the risk of CVD and whether any specific antihyperglycemic agent reduces the risk of CVD (through glycemic or other mechanisms).

The UKPDS (the United Kingdom Perspective Diabetes Study) randomly assigned subjects with newly diagnosed type 2 diabetes (n=4209) to intensive glycemic control (sulfonylurea or insulin) or conventional control (diet) with a smaller overweight subset randomized to intensive control with metformin. Significant reduction in microvascular complications were noted in the intensively treated group, but no reduction in macrovascular risk was observed, with the exception of the metformin group that showed benefit, albeit in a small group of just 342 subjects.
The ACCORD (Action to Control CardiOvascular Risk in Diabetes) trial was a large, National Health Institute (NIH)–sponsored, randomized study of 10,251 subjects with type 2 diabetes designed to determine if 3 separate strategies could reduce CV events. The glycemic intervention was to compare intensive therapy to target normal glycated hemoglobin (HbA1c) levels (<6.0%) with standard therapy to target an HbA1c of 7.0%–7.9%. The study was stopped prematurely because of increased mortality (hazard ratio [HR] 1.22; 95% confidence interval [CI], 1.01–1.46; P = 0.04) among the intensively treated group after a mean follow-up of just 3.5 years. At baseline, the ACCORD subjects had a mean age of 62.2 years, median duration of diabetes of 10 years, and mean HbA1c of 8.3%. About 35% had previous CV events and 35% were already on insulin. Despite the increased mortality, intensive glucose lowering was associated with a nonsignificant 10% reduction for the primary outcome (HR 0.90; 95% CI, 0.78–1.04; P = 0.16). After multiple analyses, no definitive explanation has yet been identified to explain the surprising mortality finding. Achieving a lower HbA1c was not associated with increased mortality. In fact, the mortality was higher in those patients in the intensive group who did not achieve a lower HbA1c. Similar adverse effects on mortality have subsequently been reported over the originally planned five years of follow-up.

The ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN modified release Controlled Evaluation) trial was a factorial, randomized, controlled international trial of 11,140 subjects with type 2 diabetes, with the glycemic intervention comparing a strategy of intensive blood glucose lowering (gliclazide-modified-release based) to target an HbA1c of 6.5% or less versus a strategy of standard glucose lowering (glibenclamide, thus suggesting that gliclazide may attenuate the progression of atherosclerosis. It has been hypothesized that the nonselective sulfonylureas, eg, glibenclamide, may have deleterious CV effects through their blockade of KATP channels in the heart and in vascular smooth muscle, which may impair ischemic preconditioning. Secondly, gliclazide also has antioxidant properties, suggesting that it may have other additional potential advantages in preventing the pathogenesis of CV complications. It has been shown that gliclazide significantly and independently reduces the progression of the carotid artery intima-media thickness compared with glibenclamide, thus suggesting that gliclazide can attenuate the progression of atherosclerosis.

Outcome trials on glycemia and cardiovascular risk – Leiter

**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACCORD</td>
<td>Action to Control CardiOvascular Risk in Diabetes</td>
</tr>
<tr>
<td>ACE</td>
<td>Acarbose Cardiovascular Evaluation</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>CV</td>
<td>cardiovascular</td>
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<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
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<tr>
<td>DPP-4</td>
<td>dipeptidyl peptidase-4</td>
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<tr>
<td>ELIXA</td>
<td>Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>GLP-1</td>
<td>glucagon-like peptide-1</td>
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<tr>
<td>HbA1c</td>
<td>glycated hemoglobin</td>
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<td>HR</td>
<td>hazard ratio</td>
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<td>MI</td>
<td>myocardial infarction</td>
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<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
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<td>ORIGIN</td>
<td>Outcome Reduction with an Initial Glargine Intervention</td>
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<tr>
<td>PROactive</td>
<td>PROspective pioglitAzone Clinical Trial In macroVascular Events</td>
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<tr>
<td>PROactive</td>
<td>PROspective pioglitAzone Clinical Trial In macroVascular Events</td>
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<tr>
<td>SAVOR-TIMI 53</td>
<td>Saxaglipitin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus—Thrombolysis In Myocardial Infarction 53</td>
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<tr>
<td>SGLT2</td>
<td>sodium-glucose cotransporter 2</td>
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<tr>
<td>SYNCHRONY</td>
<td>Effect of the Dual Peroxisome Proliferator-Activated Receptor-α/γ Agonist Aleglitazar on Risk of Cardiovascular Disease in Patients With Type 2 Diabetes</td>
</tr>
<tr>
<td>TECOS</td>
<td>Trial Evaluating Cardiovascular Outcomes with Sitagliptin</td>
</tr>
<tr>
<td>UKPDS</td>
<td>United Kingdom Prospective Diabetes Study</td>
</tr>
</tbody>
</table>

now shown that gliclazide has specific properties that may be associated with potential CV benefits. Firstly, gliclazide possesses a high selectivity for the pancreatic sulfonylurea receptor 1, suggesting optimal CV acceptability. Indeed, it has been hypothesized that the nonselective sulfonylureas, eg, glibenclamide, may have deleterious CV effects through their blockade of KATP channels in the heart and in vascular smooth muscle, which may impair ischemic preconditioning. Secondly, gliclazide also has antioxidant properties, suggesting that it may have other additional potential advantages in preventing the pathogenesis of CV complications. It has been shown that gliclazide significantly and independently reduces the progression of the carotid artery intima-media thickness compared with glibenclamide, thus suggesting that gliclazide can attenuate the progression of atherosclerosis.
Finally, the VADT (Veterans Affairs Diabetes Trial) was a multi-center trial that investigated the effects of intensive glycemic control (target HbA1c of 6% or less) compared with standard control (HbA1c 8%-9%) on CV outcomes among 1791 participants with type 2 diabetes. The choice of treatments to achieve necessary glucose targets was at the discretion of the investigator. Blood pressure and lipids were treated equally and aggressively in both groups. The primary outcome of interest was a composite of major CV events (CV death, MI, stroke, congestive heart failure, and severe inoperable coronary artery disease), amputation for ischemia, and coronary or peripheral revascularization. At baseline, the mean age was 60 years, mean duration of diabetes 11.5 years, mean HbA1c 9.4%. About 40% had a macrovascular event history. After a mean follow-up of 5 years, there was no difference in the primary outcome between the groups (25.9% intensive versus 29.3% standard; HR 0.87; P=0.12) and importantly, no difference in mortality. No difference was found in any of the various CV secondary outcomes.

There have been several meta-analyses of these trials. Perhaps the most informative is that done by the Control Group. This analysis was performed by the investigators of these trials who were thus able to use a common end point definition and to truncate the results of the UKPDS to have a similar duration of follow-up as the other trials. Overall, intensive glycemic

### Table: Outcome Trials on Glycemia and Cardiovascular Risk

<table>
<thead>
<tr>
<th>Trials</th>
<th>More intensive</th>
<th>Less intensive</th>
<th>ΔHbA1c (%)</th>
<th>Favors more intensive</th>
<th>Favors less intensive</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major cardiovascular event</td>
<td>ACCORD 352 (2.11)</td>
<td>371 (2.29)</td>
<td>-1.01</td>
<td></td>
<td></td>
<td>0.90 (0.78-1.04)</td>
</tr>
<tr>
<td></td>
<td>ADVANCE 557 (2.15)</td>
<td>590 (2.28)</td>
<td>-0.72</td>
<td></td>
<td></td>
<td>0.94 (0.84-1.06)</td>
</tr>
<tr>
<td></td>
<td>UKPDS 169 (1.30)</td>
<td>87 (1.60)</td>
<td>-0.66</td>
<td></td>
<td></td>
<td>0.80 (0.62-1.04)</td>
</tr>
<tr>
<td></td>
<td>VADT 116 (2.68)</td>
<td>128 (2.98)</td>
<td>-1.16</td>
<td></td>
<td></td>
<td>0.90 (0.70-1.16)</td>
</tr>
<tr>
<td>Overall</td>
<td>1194</td>
<td>1176</td>
<td>-0.88</td>
<td></td>
<td></td>
<td>0.91 (0.84-0.99)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>ACCORD 198 (1.18)</td>
<td>245 (1.51)</td>
<td>-1.01</td>
<td></td>
<td></td>
<td>0.77 (0.64-0.93)</td>
</tr>
<tr>
<td></td>
<td>ADVANCE 310 (1.18)</td>
<td>337 (1.28)</td>
<td>-0.72</td>
<td></td>
<td></td>
<td>0.92 (0.79-1.07)</td>
</tr>
<tr>
<td></td>
<td>UKPDS 150 (1.20)</td>
<td>76 (1.40)</td>
<td>-0.66</td>
<td></td>
<td></td>
<td>0.81 (0.62-1.07)</td>
</tr>
<tr>
<td></td>
<td>VADT 72 (1.65)</td>
<td>87 (1.99)</td>
<td>-1.16</td>
<td></td>
<td></td>
<td>0.83 (0.61-1.13)</td>
</tr>
<tr>
<td>Overall</td>
<td>730</td>
<td>745</td>
<td>-0.88</td>
<td></td>
<td></td>
<td>0.85 (0.76-0.94)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>ACCORD 135 (0.79)</td>
<td>94 (0.56)</td>
<td>-1.01</td>
<td></td>
<td></td>
<td>1.35 (1.04-1.76)</td>
</tr>
<tr>
<td></td>
<td>ADVANCE 253 (0.95)</td>
<td>289 (1.08)</td>
<td>-0.72</td>
<td></td>
<td></td>
<td>0.88 (0.74-1.04)</td>
</tr>
<tr>
<td></td>
<td>UKPDS 71 (0.53)</td>
<td>29 (0.52)</td>
<td>-0.66</td>
<td></td>
<td></td>
<td>1.02 (0.66-1.57)</td>
</tr>
<tr>
<td></td>
<td>VADT 38 (0.83)</td>
<td>29 (0.63)</td>
<td>-1.16</td>
<td></td>
<td></td>
<td>1.32 (0.81-2.14)</td>
</tr>
<tr>
<td>Overall</td>
<td>497</td>
<td>441</td>
<td>-0.88</td>
<td></td>
<td></td>
<td>1.10 (0.84-1.42)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>ACCORD 257 (1.41)</td>
<td>203 (1.14)</td>
<td>-1.01</td>
<td></td>
<td></td>
<td>1.22 (1.01-1.46)</td>
</tr>
<tr>
<td></td>
<td>ADVANCE 498 (1.86)</td>
<td>533 (1.99)</td>
<td>-0.72</td>
<td></td>
<td></td>
<td>0.93 (0.83-1.06)</td>
</tr>
<tr>
<td></td>
<td>UKPDS 123 (0.13)</td>
<td>53 (0.25)</td>
<td>-0.66</td>
<td></td>
<td></td>
<td>0.96 (0.70-1.33)</td>
</tr>
<tr>
<td></td>
<td>VADT 102 (2.22)</td>
<td>95 (2.06)</td>
<td>-1.16</td>
<td></td>
<td></td>
<td>1.07 (0.81-1.42)</td>
</tr>
<tr>
<td>Overall</td>
<td>980</td>
<td>884</td>
<td>-0.88</td>
<td></td>
<td></td>
<td>1.04 (0.90-1.20)</td>
</tr>
</tbody>
</table>

Figure 1. Meta-analysis of more intensive vs less intensive glycemic control.

This meta-analysis was undertaken with the goal of more precisely estimating the effects of more intensive vs less intensive glucose control on the risk of major cardiovascular events in subjects with type 2 diabetes and included the four major randomized controlled trials investigating these effects (ACCORD, ADVANCE, UKPDS, and VADT). A total of 27 049 participants and 2370 events contributed to the meta-analysis. Compared with less intensive glucose control, more intensive glucose control was associated with a 9% reduced risk of major cardiovascular events (hazard ratio [HR] 0.91; 95% confidence interval [CI], 0.84-0.99). This was attributed largely to a reduced risk of myocardial infarction (relative risk reduction 15%; HR 0.85; 95% CI, 0.76-0.94). Mortality was not significantly different between the two groups. Thus, the increased mortality associated with intensive glucose control that was observed in the ACCORD trial was not confirmed in this meta-analysis.

Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation; HbA1c, glycated hemoglobin; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

control was associated with significant reductions in major CV events (HR 0.91; 95% CI, 0.87-0.99), and myocardial infarctions (HR 0.85; 95% CI, 0.76-0.94) (Figure 1). There was no overall increase or decrease in all-cause mortality (HR 1.04; 95% CI, 0.90-1.20). Significant heterogeneity for CV events was observed based on history of macrovascular disease (Figure 2). A significant 16% reduction was observed in those in whom it was absent (HR 0.84; 95% CI, 0.75-0.94) while no effect (HR 1.00; 95% CI, 0.89-1.13) was observed in whom it was present. Other subgroups including age, baseline HbA1c, and duration of diabetes did not show any heterogeneity.

Another important recent publication was that of the posttrial follow-up of UKPDS. Patients were followed for an additional 10 years after completion of the randomized phase of the trial. Despite the fact that within-trial differences in HbA1c between intensive therapy and conventional therapy disappeared fairly quickly, those individuals who were originally assigned to the intensive therapy group continued to show vascular benefit, a phenomenon that has been called the "legacy effect" (Table I). A similar phenomenon had been previously described in patients with type 1 diabetes in the extended follow-up of the DCCT (Diabetes Control and Complications

### Table I. UKPDS: legacy effect of earlier glucose control

<table>
<thead>
<tr>
<th>Aggregate end point</th>
<th>1997</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes-related end point</td>
<td>12%</td>
<td>9%</td>
</tr>
<tr>
<td>P</td>
<td>0.029</td>
<td>0.040</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>25%</td>
<td>24%</td>
</tr>
<tr>
<td>P</td>
<td>0.0099</td>
<td>0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>16%</td>
<td>15%</td>
</tr>
<tr>
<td>P</td>
<td>0.052</td>
<td>0.014</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>6%</td>
<td>13%</td>
</tr>
<tr>
<td>P</td>
<td>0.44</td>
<td>0.007</td>
</tr>
</tbody>
</table>

P, log-rank; RRR, relative risk reduction

After a median 8.5 years' posttrial follow-up (intensive sulfonylurea/insulin therapy vs conventional therapy). With more than 66 000 person-years of follow-up, this large posttrial study showed that benefits of an intensive strategy to control blood glucose levels in patients with type 2 diabetes were sustained for up to 10 years after the cessation of randomized interventions. Benefits persisted despite the early loss of within-trial differences in glycated hemoglobin levels between the intensive-therapy group and the conventional-therapy group—a so-called legacy effect. The trial showed the extended effects of improved glycemic control in patients with newly diagnosed type 2 diabetes, some of whom were followed for up to 30 years. The trial also showed that there were differences in outcomes between an intensive glucose control strategy using sulfonylureas or insulin and that using metformin in overweight patients.

Trial) in which it was termed “metabolic memory.” Another lesson from the extended follow-up of the UKPDS is that the benefits of intensive glycemic control may take many years to translate into CV benefit, unlike lipid or blood pressure trials in which the benefits are typically seen within 3-5 years. Thus, there are several lessons from the CV outcome studies completed to date. Early intervention (such as what was done in the UKPDS) may be associated with greater vascular benefit and the benefits may be greater in those individuals without a prior history of CVD. Furthermore, it may take many years of good glycemic control to translate into CV risk reduction. These conclusions should be kept in mind when one considers the design of the ongoing clinical trials (as discussed below).

Another key question is whether any specific antihyperglycemic agent reduces the risk of CVD. A substudy of the UKPDS looked at metformin in their overweight patients and, compared with the conventional policy, the use of metformin was associated with a 32% risk reduction in any diabetes-related end points, 42% risk reduction in diabetes-related deaths, 36% risk reduction in all-cause mortality, and 39% risk reduction in myocardial infarction, all of which were statistically significant. However, given the small number of study subjects in this group, these results, although suggestive of CV benefit of metformin, cannot be considered definitive. The PROactive (PROspective pioglitAzone Clinical Trial in macroVascular Events) study showed that overall there was no significant difference between the addition of pioglitazone versus placebo on top of background antihyperglycemic agents on a very broad composite primary end point consisting of death, nonfatal myocardial infarction, all of which were statistically significant. However, given the small number of study subjects in this group, these results, although suggestive of CV benefit of metformin, cannot be considered definitive. The PROactive (PROspective pioglitAzone Clinical Trial in macroVascular Events) study showed that overall there was no significant difference between the addition of pioglitazone versus placebo on top of background antihyperglycemic agents on a very broad composite primary end point consisting of death, nonfatal myocardial infarction, stroke, acute coronary syndrome, leg amputation, and coronary vascularization or leg revascularization. The so-called “principal secondary end point,” consisting of the more traditional major adverse CV events (nonfatal myocardial infarction, stroke, and CV mortality) was, however, reduced by a significant 12%. Thus, once again, the results can be considered suggestive, but not definitive for the CV benefit of an antihyperglycemic agent. In fact, the United States Food and Drug Administration (FDA) stated in 2009 that “no antihyperglycemic agent has been shown to significantly reduce the risk of vascular disease.”

The controversy as to whether rosiglitazone was associated with increased CV risk or not, largely spurred by the meta-analysis of Nissen and Wolski published in 2007, prompted the FDA in 2008 to publish a new guidance for industry on evaluating CV risk in new antihyperglycemic therapies to treat type 2 diabetes. They declared that as part of the approval process for diabetes medicines, a postmarketing trial would generally be necessary to definitely show that the upper bound of the two-sided 95% CI for the estimated risk ratio is <1.3. Largely as a result of this guidance, a large number of CV outcome trials are currently underway testing new antihyperglycemic agents. The results of the ORIGIN study (Outcome Reduction with an Initial Glargine Intervention), testing the effects of insulin glargine on CV outcomes, were recently published. This trial included 12,537 subjects 50 years of age or older with either early type 2 diabetes or prediabetes who were randomly assigned to receive titrated basal insulin glargine with a target fasting plasma glucose <5.3 mmol/L or standard of care. Overall, the glargine had a neutral effect on the two coprimary composite CV end points.

There are a large number of ongoing clinical trials utilizing the incretin agents (glucagon-like peptide-1 [GLP-1] receptor agonists and dipeptidyl peptidase-4 [DPP-4] inhibitors) (www.clinicaltrials.gov). There are a number of potential mechanisms by which the incretins may reduce CV risk. Firstly, they have beneficial effects on glycemia, body weight (more so with the GLP-1 receptor agonists than DPP-4 inhibitors), blood pressure, and lipid profile, especially postprandial lipemia. In addition, there is evidence to suggest that these drugs may have other, more direct, cardiac benefits. Although much of this is based on animal models of diabetes, there are now limited human studies that have also suggested that the incretins may also improve cardiac function and minimize ischemic damage. Although it might be expected that the GLP-1 receptor agonists which raise levels of GLP-1 to a greater degree may be associated with greater potential CV benefit, the DPP-4 inhibitors also increase a number of other substrates, including stromal cell-derived factor-1, which may also directly or indirectly regulate CV function, and thus may have other mechanisms by which they can reduce CV risk.

There are suggestions from clinical trials completed to date that the use of the incretin agents may, indeed, be associated with reduced CV risk. In the registration trials with the DPP-4 inhibitors linagliptin, saxagliptin, and sitagliptin, as well as the GLP-1 receptor agonists exenatide and liraglutide, the use of these agents was associated with a 30%-57% reduced risk of CV events relative to comparator. Although the number of CV events in each of these trials was not large, the consistency of the results is promising. Furthermore, recent meta-analyses by Monami and colleagues, looking at the various trials with GLP-1 receptor agonists and DPP-4 inhibitors versus all comparators as well as placebo, also suggested CV benefits. These studies cannot, however, be considered definitive.

There are four ongoing clinical trials with DPP-4 inhibitors. Three of them are comparing DPP-4 inhibitors with placebo: the EXAMINE (EXamination of cArdiovascular outcoMes: alogliptin vs standard of care in patients with type 2 diabetes mellitus and acute coronary syndrome) study with alogliptin, the SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus—Thrombolysis In Myocardial Infarction 53) with saxagliptin, and TEOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) with sitagliptin. They are being conducted in somewhat different
study populations. EXAMINE includes about 5400 subjects with a recent acute coronary syndrome, SAVOR-TIMI 53 includes about 16 500 subjects (about two-thirds of whom have prior history of CVD and the others two or more CV risk factors apart from their diabetes), and TECOS includes about 14 000 patients with established CVD. The CAROLINA (Cardiovascular outcome study of Linagliptin versus glimepiride in patients with type 2 diabetes) study is the only one of the incretin trials that has an active comparator. The potential CV benefit of linagliptin is being compared with the sulfonylurea glimepiride in about 6000 patients with known CVD or two or more risk factors.

There are also four ongoing clinical trials with GLP-1 receptor agonists. All are compared with placebo as add-on to background antihyperglycemic agents. ELIXA (Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010) is utilizing lixisenatide, EXSCEL (EXenatide Study of Cardiovascular Event Lowering) is using once-weekly exenatide, LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results) is using liraglutide, and REWIND (Researching cardiovascular Events with a Weekly INcretin in Diabetes) is using dulaglutide. While ELIXA is being carried out in patients with a recent acute coronary syndrome, the other studies are being done in individuals with known vascular disease or multiple risk factors in addition to diabetes. The sample sizes of these trials are expected to range from 6000-10 000.

Treatment with the sodium-glucose cotransporter 2 (SGLT2) inhibitors has been associated with reductions in blood pressure and body weight in addition to glucose lowering, and therefore their use may also be expected to potentially reduce CV risk. The CANVAS study (CANagliflozin cardioVascular Assessment Study) is looking at the effects of canagliflozin in about 4300 individuals with type 2 diabetes and a history of or who are at high risk for CVD, and C-SCADE 8 (BI 10773 Add-On to Usual Care Compared With Usual Care Alone in Patients With Type 2 Diabetes Mellitus at High Cardiovascular Risk) is comparing empagliflozin with usual care alone in patients with type 2 diabetes and known vascular disease.

The dual peroxisome proliferator-activated receptor agonist aleglitazar has been shown to have beneficial effects on both glucose levels and lipids. In the 16-week SYNCHRONY study (Effect of the Dual Peroxisome Proliferator-Activated Receptor-α/γ Agonist Aleglitazar on Risk of Cardiovascular Disease in Patients With Type 2 Diabetes), the 0.15-mg dose was associated with a 0.85% reduction in HbA1c, 43.4% reduction in triglycerides, 15.5% reduction in low-density lipoprotein cholesterol, and a 20.7% increase in high-density lipoprotein cholesterol. Therefore, in a phase 3 study called ALECARDIO (Cardiovascular Outcomes Study to Evaluate the Potential of Aleglitazar to Reduce Cardiovascular Risk in Patients With a Recent Acute Coronary Syndrome (ACS) Event and Type 2 Diabetes Mellitus), the addition of aleglitazar 0.15 mg versus placebo added to standard of care is being compared in about 6000 subjects with diabetes post–acute coronary syndrome.

Finally, in the STOP NIDDM trial (Study TO Prevent Non-Inulin-Dependent Diabetes Mellitus), acarbose was associated with a significant reduction in CV events and new-onset hypertension, although the number of events was very small. The ongoing ACE (Acarbose Cardiovascular Evaluation) study is testing the addition of acarbose versus placebo in patients with established coronary heart disease or acute coronary syndrome in about 7500 subjects with impaired glucose tolerance over the age of 50.

Conclusion
There is evidence from large randomized controlled trials that improved glycemic control may be associated with a reduced risk for CVD, but that this benefit may be greater in individuals with a shorter duration of diabetes and with no prior history of CVD. At the same time, there is no definitive evidence that any specific antihyperglycemic agent is associated with CV benefit, although there has been a suggestion of benefit for metformin in the UKPDS, gliclazide-based therapy in ADVANCE, and pioglitazone in PROactive.

As a result of new FDA regulations, a number of ongoing studies will provide us much additional information on specific agents. These trials will certainly provide important 3- to 5-year safety data on new agents, which should be sufficient to rule out CV harm and may also provide data on unanticipated safety issues (eg, the neutral effect of glargine on cancer observed in ORIGIN). The exposure will likely not be sufficient (not enough subjects entered and/or inadequate duration of follow-up) to rule out less common adverse effects. These studies may or may not show benefits of specific agents to reduce CV risk. Furthermore, any difference in benefits seen with the various agents may be related not to inherent differences among the drugs, but perhaps to differences in the duration of follow-up, protocol design, comparator, or study population (presence versus absence of known CVD). These studies may also provide other novel information about diabetes. Finally, although the cost of these large studies is significant, this does not appear to have hampered the development of new antihyperglycemic agents, notwithstanding initial concerns to the contrary.

Acknowledgment: The editorial assistance of Hwee Teoh, PhD is greatly appreciated.
Keywords: antihyperglycemic agent; cardiovascular disease; DPP-4 inhibitor; GLP-1 receptor agonist; glycemic control; insulin; metformin; SGLT2 inhibitor; sulfonylurea; type 2 diabetes mellitus
ÉTUDES DE RÉSULTATS DES EFFETS DU CONTRÔLE GLYCÉMIQUE SUR LE RISQUE CARDIOVASCULAIRE DANS LE DIABÈTE DE TYPE 2.
QUE SAVONS-NOUS ET QUE POUVONS-NOUS APPRENDRE DES ÉTUDES EN COURS ?

D’après les données de récentes études randomisées et contrôlées à grande échelle, un meilleur contrôle glycémique diminuerait le risque de développer une maladie cardiovasculaire, notamment chez les patients dont le diabète est plus récent et qui ne présentent pas d’antécédent de maladie cardiovasculaire. L’augmentation encore inexpliquée de la mortalité observée dans l’étude ACCORD n’a pas été retrouvée dans d’autres études. Il n’a pas encore été démontré avec certitude qu’un agent antihyperglycémique puisse être associé à une protection cardiovasculaire, bien que des bénéfices aient été liés à l’administration de metformine dans l’étude UKPDS (United Kingdom Prospective Diabetes Study), de gliclazide dans l’étude ADVANCE (Action in Diabetes and Vascular disease : PreterAx and Dia-microN MR Controlled Evaluation) et de pioglitazone dans l’étude PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events). À la suite des nouvelles réglementations de la FDA (Federal Drug Administration), de nombreuses études sont actuellement en cours qui nous apporteront des informations supplémentaires sur des molécules spécifiques. Ces études fourniront des données importantes sur la sécurité d’emploi de ces nouvelles molécules sur 3 à 5 ans, mais n’apporteront peut-être pas de réponses quant à leur capacité à réduire les risques cardiovasculaires. En outre, toute différence dans les résultats observée avec ces molécules distinctes pourrait être liée à la conception des études ou aux populations étudiées plus qu’à des différences propres aux molécules elles-mêmes.
Glucose lowering and kidney protection: can we hit 2 birds with 1 stone?

by M. E. Cooper, Australia

Epidemiological as well as clinical trial data have emphasized the central role of glucose in promoting microvascular complications, including diabetic nephropathy. Over the last 20 years, the mechanisms for such glucose-promoted development of renal complications have been extensively investigated and well described. Recent data from the ADVANCE trial (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation) demonstrates powerful effects of improving glycemic control with a gliclazide MR–based regimen on a range of renal end points, including urinary albumin excretion and the development of end-stage renal disease. It is likely that the best approach to retard or reverse diabetic nephropathy will involve a multifactorial approach which includes not only glucose-lowering agents, but also therapies that address other risk factors such as hypertension. These studies emphasize not only the importance of glycemic control in the development and progression of diabetic complications, including nephropathy, but also highlight the role of therapies that improve glycemic control in retarding diabetic kidney disease.

Historically, the diagnosis of diabetes has been based on the level of hyperglycemia that is associated with the development of microvascular complications, including nephropathy.1 Thus, there has been a long-standing view that hyperglycemia per se is directly linked to the pathogenesis and progression of diabetic nephropathy. Initial observational studies, including the seminal findings by Pirart, clearly demonstrated that elevated glucose levels were associated with an increased prevalence of a range of diabetic complications.2 Subsequent studies, such as the landmark trial DCCT (Diabetes Control and Complications Trial) and its follow-up study EDIC (Epidemiology of Diabetes Interventions and Complications), clearly showed that intensified glycemic control had a sustained beneficial effect on the development of diabetic nephropathy.3,4 These findings were observed in cohorts of type 1 diabetic subjects with or without microvascular complications at the time of randomization.

A more recent analysis of the EDIC cohort confirms long-term renal benefits of prior intensification of glycemic control with a lower glomerular filtration rate in those subjects in the conventionally treated groups.5 However, that study was underpowered to determine if this improvement in renal end points would ultimately lead to less end-stage kidney disease.
The UKPDS (United Kingdom Prospective Diabetes Study) clearly showed that in a group of newly diagnosed type 2 diabetic subjects there were significant benefits to optimizing glycemic control with sulfonylurea- and insulin-based regimens on various microvascular complications, including nephropathy. However, the appropriate thresholds for instituting intensification of glycemic control and the appropriate contemporary glycemic targets, specifically in terms of glycosated hemoglobin (HbA1c), that clinicians should achieve to reduce the development and progression of nephropathy were not known. Thus, studies such as the ADVANCE trial (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation), as outlined below, were instituted to address these questions.

Over the last 20 years, there has been a significant advance in our understanding of how glucose itself promotes renal damage (Figure 1). It is clear that not only does hyperglycemia play a key role in promoting renal injury, but glucose appears to interact with other stimuli, such as hemodynamic factors clinically manifesting as systemic hypertension, to enhance damage of the various heterogeneous cell populations within the kidney.

Glucose promotes the generation of reactive oxygen species which activate intracellular signaling molecules and enhance expression of growth factors and cytokines in mediating diabetic complications.

**Figure 1.** Schema outlining interactions among hemodynamic factors, metabolic pathways, intracellular signaling molecules, and cytokines in mediating diabetic complications.

**Abbreviations:** CTGF, connective tissue growth factor; NF-kB, nuclear factor κB; TGF-β, transforming growth factor β.

The ADVANCE study has been able to directly address the relative roles of blood pressure and glucose-lowering therapies in retarding and potentially reversing complications as a result of type 2 diabetes. This multinational, multiethnic study of over 11 000 type 2 diabetic subjects included a glucose control arm which involved a stepped-care approach based on first-line antidiabetic therapy with the sulfonylurea gliclazide and dipeptidyl peptidase-4 inhibitors. In this study using conventional approaches to optimize glycemic control, which was able to achieve over several years a net reduction in HbA1c of approximately 0.7%, it was possible to specifically test if a reduction in HbA1c would translate to a reduction in renal end points.

In the initial analysis, microvascular end points including nephropathy were included as a component of the primary end point of the study, which was a composite end point of both microvascular and macrovascular complications. Further analysis revealed that the major effect of improved glycemic control was on microvascular end points with additional exploration of the major findings of the study emphasizing benefits on renal rather than retinal outcomes. Specifcally, there was a 21% decrease in new-onset nephropathy, defined as a composite of the development of macroalbuminuria, doubling of serum creatinine to equal or greater than 200 µM, the need
for renal replacement therapy, and death due to renal disease (Figure 2). The major effect appeared to be the 30% decrease in development of macroalbuminuria. Furthermore, an additional renal secondary end point was the 9% decrease in development of microalbuminuria. This effect on microalbuminuria was further examined, and, indeed, not only was there a 10% reduction in progression of albuminuria, but also a 15% increase in regression, as defined by a reduction in albuminuria from the microalbuminuric to the normoalbuminuric range. Furthermore, detailed analyses are currently being performed with preliminary results indicating a >50% decrease in end-stage kidney disease. Thus, it is clear that improvements in glycemic control have effects on prevention of early renal disease, as reflected by a reduction in microalbuminuria and a retardation in the progression from early to advanced renal disease, as defined by a decrease in progression to macroalbuminuria and/or end-stage kidney disease.

In the ADVANCE study, a close relationship between albuminuria and cardiovascular disease was identified. Not only an increase in baseline, but also an elevation in achieved urinary albumin excretion was associated with a higher risk of cardiovascular disease. Thus, it is clear that improvements in glycemic control have effects on prevention of early renal disease, as reflected by a reduction in microalbuminuria and a retardation in the progression from early to advanced renal disease, as defined by a decrease in progression to macroalbuminuria and/or end-stage kidney disease.

The positive effects on microvascular complications seen in the ADVANCE study have also been seen in other clinical trials performed concurrently involving intensification of glycemic control. In the VADT (Veterans Affairs Diabetes Trial), optimization of glycemic control led to a reduction in urinary albumin excretion. Similar positive effects were seen in the ACCORD study (Action to Control Cardiovascular Risk in Diabetes) with intensified glycemic control leading to a delay in the onset of microalbuminuria. A recent meta-analysis has summarized the effects of improved glycemic control on renal end points. Indeed, these benefits were sustained during follow-up after 13 years despite a 5-year return to less intensified conventional therapies associated with not only reduced cardiovascular events, but a decrease in overall mortality.

Although this report has focused on the glucose arm of the ADVANCE study, it needs to be appreciated that the development of diabetic complications is multifactorial in origin with...
blood pressure also playing a key role in the susceptibility to and rate of progression of diabetic complications including nephropathy.\(^5\) Indeed, blood pressure reduction using a perindopril/indapamide-based regimen was very effective at reducing renal events.\(^25\) Furthermore, subsequent analysis revealed a close correlation between renal events and achieved systolic blood pressure.\(^26\) Recent analyses have been performed to assess the relative contributions of improvements in glycemic control and blood pressure on mortality and diabetic complications in the ADVANCE trial. Indeed, particularly with respect to nephropathy, both interventions had similar beneficial effects on renal end points with the combination of intensified glycemic control and antihypertensive therapy having additive effects on diabetic renal disease (Figure 3).\(^27\) This concept of multifactorial intervention has been previously demonstrated in the Steno-2 study where a regimen involving lipid-, glucose-, and blood pressure–lowering therapies was particularly effective at retarding microvascular and macrovascular complications, ultimately translating to a >50% decrease in mortality.\(^13\)

The importance of these findings needs to be considered in the context of the rapid worldwide increase in type 2 diabetes, continuing to lead to further growth in the number of people requiring renal replacement therapies, including dialysis. Much of the increase in type 2 diabetes and associated end-stage renal failure is occurring in less affluent countries where renal replacement therapies\(^28\) such as dialysis or renal transplantation are not widely available. Therefore, in these less developed countries, the development of end-stage renal failure essentially represents a death sentence.\(^29\) Indeed, the ability to significantly slow down progression of renal disease using relatively inexpensive and predominantly oral-based antidiabetic regimens, as documented in the ADVANCE population with one-third of its subjects being of Asian origin, provides an opportunity for clinicians to reduce the burden of renal disease in the type 2 diabetic population. Even in settings where renal replacement therapy is available, deferring ESRD and in certain contexts promoting regression of diabetic nephropathy represents a major advance in renoprotection, reducing the morbidity and mortality associated with type 2 diabetes.

References
\(^{17.}\) Gaede P, Vedel P, Parving HH, Pedersen O. Intensified multifactorial interven-


**Keywords:** end-stage renal disease; glycemic control; diabetic nephropathy; HbA1c; type 2 diabetes

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**BAISSÉ GLYCÉMIQUE ET PROTECTION RÉNALE : POUVONS-NOUS FAIRE D’UNE PIERRE DEUX COUPS ?**

Les études cliniques et épidémiologiques ont souligné le rôle central du glucose dans la survenu des complications microvasculaires, dont la néphropathie diabétique. Les mécanismes responsables des complications rénales liées au glucose ont été abondamment explorés et décrits ces 20 dernières années. La récente étude ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation) a démontré la grande efficacité du contrôle glycémique par le gliclazide LM sur des critères rénaux comme l’albuminurie et le développement de l’insuffisance rénale terminale. La meilleure façon de retarder l’apparition d’une néphropathie diabétique ou de la faire régresser est probablement d’employeur une approche multifactorielle basée sur des hypoglycémiants, mais aussi sur le traitement d’autres facteurs de risque tels que l’hypertension. Ces études montrent non seulement l’importance du contrôle glycémique dans le développement et la progression des complications diabétiques comme la néphropathie, mais mettent aussi en avant le rôle des traitements améliorant ce contrôle qui retardent l’apparition de l’insuffisance rénale diabétique.
The legacy effect in type 2 diabetes: fact or fiction?

by M. Marre, France

Diabetes is a lifelong disease; thus, it is of utmost importance that we understand the “legacy effect” of long-term interventions on vascular outcomes. Intervention studies conducted many years ago on the diabetic retinal disease in type 1 diabetes gave rise to the concept of “memory effect” in uncontrolled diabetes. A long-term effect of high glucose levels on the functions and structure of vessels, with an impact on outcomes, is biologically plausible. In particular, interventions for glycemic control may lead, in the long term, to a benefit in terms of risk for premature death, as shown in the UKPDS (United Kingdom Prospective Diabetes Study). Interestingly, this legacy effect does not apply to high glucose only, but also to other vascular risk factors, such as hypertension and lipids. As many factors can influence final outcomes over a lifetime, it is important to set up prospective follow-up studies of participants in large vascular clinical trials. However, the duration of follow-up must be long enough to be clinically meaningful. Such considerations lead to implementation of the ADVANCE-ON study (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation post-trial ObservatioNal study), expected to provide important follow-up data in type 2 diabetes patients in a contemporary diabetes management setting.

The concept of a glucose “legacy effect” (initially called “memory effect”) emerged from the first trial on the effect of strict glycemic control in retinopathy in patients with insulin-dependent diabetes and background retinopathy. In this single-center, open-label, randomized trial, participants allocated to continuous subcutaneous insulin infusion had poorer retinal status than those on conventional insulin treatment over a six-month period, although they had improved albumin excretion rates (AER). This intergroup difference vanished, however, after one year. Similar findings were later observed in the DCCT (Diabetes Control and Complications Trial) among participants with background retinopathy at baseline, during the first two years of the trial. From these data came the concept that the body could essentially “remember” long periods with high glucose, and this was called the “memory effect.” This term was later substituted by “legacy effect” when the results of the ten-year follow-up of the UKPDS study were issued.

Since then, questions have arisen with regard to the legacy effect of glucose on vascular outcomes in clinical diabetes. Is the legacy effect permanent or reversible? Would late intervention to control high glucose have an effect on outcomes, especially once diabetes has continued uncontrolled long enough to cause deterioration of vessels? Does the legacy effect apply to some complications (retinal), but not to others (renal)? …Let’s take a closer look at the legacy effect and some of these questions.”
cially once diabetes has continued uncontrolled long enough to cause deterioration of vessels? Does the legacy effect apply to some complications (retinal), but not to others (renal)? Is there a biological precedent for such a phenomenon? Is this phenomenon specific to glucose, or is it observable with other risk factors? What are the practical issues for the different treatment strategies? Here, let’s take a closer look at the legacy effect and some of these questions.

Summary of legacy effects observed in diabetes

Legacy effects were first observed in type 1, insulin-dependent diabetes during the DCCT and its posttrial follow-up, EDIC (Epidemiology of Diabetes Interventions and Complications). These observations illustrated that glucose memory may have both negative and positive effects.

As an illustration of a negative effect, let’s look once again to the principal data of the DCCT.3 The participants were randomized into intensive versus conventional treatment with a factorial design; half of them had no retinopathy at baseline, and half of them had background retinopathy. In those with background retinopathy who were allocated to the intensive arm, retinal status deteriorated slightly up to the third year (although this deterioration was not severe enough to warrant termination of the trial). Afterwards, this memory effect vanished; however, consequently, the final benefit (relative risk reduction) over a 6.5-year period was lower than in those participants without retinopathy at baseline (Figure 1).

In contrast, most of the follow-up studies published thus far on the DCCT-EDIC study illustrate well a positive effect from memory of a long period with strict glycemic control. First, the carotid intima-media thickness of participants allocated to intensive treatment progressed less than in the control group several years after the end of the study, while mean HbA1c had regressed to an identical mean value for the two groups.6 Second, the intensive group displayed significantly fewer cardiovascular events during follow-up than the control group, with an impressive risk reduction of around 50%.7 Notably, a 41% risk reduction in cardiovascular events was detectable by the end of the DCCT, although numbers were not high enough to reach statistical significance.3 Third, the risk for impaired glomerular filtration rate in the intensive treatment group was reduced by 50% in the long term, compared with the control group.

**Figure 1. Impact of strict glycemic control in the participants of the DCCT.**

A sustained change in the severity of retinopathy was defined as a change observed by fundus photography of at least three steps from baseline that was sustained for at least six months. A, Primary-prevention cohort. B, Secondary-intervention cohort. The numbers of patients evaluated in each therapy group are indicated below the graphs. Note the initially negative impact of strict glycemic control on the course of retinopathy in the participants with baseline background retinopathy (Panel B).

**Abbreviation:** DCCT, Diabetes Control and Complications Trial.


**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>ACCORD</td>
<td>Action to Control CardiOvascular Risk in Diabetes</td>
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<td>ADVANCE ON</td>
<td>Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation posttrial ObservatioNal study</td>
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<tr>
<td>AER</td>
<td>albumin excretion rate</td>
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<td>AGE</td>
<td>advanced glycation end product</td>
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<td>DCCT</td>
<td>Diabetes Control and Complications Trial</td>
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<tr>
<td>EDIC</td>
<td>Epidemiology of Diabetes Interventions and Complications</td>
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<tr>
<td>GBM</td>
<td>glomerular basement membrane</td>
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<tr>
<td>HbA1c</td>
<td>glycated hemoglobin</td>
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<td>HOPE</td>
<td>Heart Outcomes Prevention Evaluation</td>
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<td>HOPE-TOO</td>
<td>HOPE-The Ongoing Outcomes</td>
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<td>O2</td>
<td>superoxide anion</td>
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<td>UKPDS</td>
<td>United Kingdom Prospective Diabetes Study</td>
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<td>WOSCOP</td>
<td>West Of Scotland Coronary Prevention study</td>
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Figure 2. The legacy effect of intensified glycemic control in the UKPDS. Hazard ratios for patients in the UKPDS who had any diabetes-related end point (A and B), myocardial infarction (C and D), or microvascular disease (E and F) or who died from any cause (G and H) are shown for the sulfonylurea-insulin group versus the conventional-therapy group and for the metformin group versus the conventional-therapy group. The overall values at the end of the study, in 1997, are shown (red squares), along with the annual values during the 10-year posttrial monitoring period (blue diamonds). Hazard ratios below unity indicate a favorable outcome from sulfonylurea or metformin therapy. Numbers of first events in an aggregate outcome that accumulated in each group are shown at 2-year intervals. The vertical bars represent 95% confidence intervals.

Abbreviation: UKPDS, United Kingdom Prospective Diabetes Study.

group. Finally, the above-mentioned benefits in the long term were not counterbalanced by any impairment in the cognitive functions of the participants, which could have resulted from a 3-fold higher number of severe hypoglycemic episodes.

In type 2 diabetes, all data available as regards legacy effect were generated from the UKPDS study. In the glucose arm of this open-label, multicenter, national study, the 0.9% HbA1c difference between the intensive treatment (based on the use of sulfonylureas or insulin) and the conventional one (dietary intervention only) produced a significant 25% risk reduction for microvascular outcomes, but no significant effect on risk for myocardial infarction, stroke, or death from any cause. Ten years after the study’s end, this group reported the same outcomes for the 10-year follow-up. The relative risk reductions observed in the initial report were sustained or improved in the follow-up period, and the long follow-up with much higher number of events revealed substantial and statistically significant benefits. The most important benefit concerned the rate of death from any cause (Figure 2, page 55). Otherwise, most intergroup hazard ratios remained stable throughout the observation period.

Another study in type 2 diabetics, ACCORD (Action to Control Cardiovascular Risk in Diabetes), was terminated prematurely in February 2008, because the rate of total mortality (including cardiovascular mortality) was higher in the experimental group than in the control group. Parenthetically, this result on the impact of intensive glycemic control in type 2 diabetes was not confirmed by the meta-analysis of this outcome in all individual participants of the four major trials in this domain: UKPDS, ADVANCE, ACCORD, and VADT (Veterans Affairs Diabetes Trial). Because the ACCORD participants were also randomized to lipid-lowering, and to blood pressure-lowering studies, they were followed-up accordingly, in ACCORD-ON, for the outcome of the glucose arm of the study until June 2009, the originally planned end. Data collected during the 16-month extra follow-up were similar to the initially published data. However, the follow-up period was probably too short to eliminate the concerns that led to the early termination of the ACCORD trial, from a methodological viewpoint.

**Legacy effect: permanent and applicable to all diabetes-related outcomes?**

As mentioned earlier, a negative memory effect on retinal condition was reported to vanish in participants of the first trial for which this phenomenon was reported. Moreover, the effect on AER was beneficial from the first six months of the study. However, the AER is a functional parameter, not an anatomical one, nor an outcome per se.

This issue of functional versus anatomical definitions of complications is well illustrated by the studies conducted by Mauer et al: in 1975, Mauer reported that the anatomical signs of diabetic nephropathy (increased width of the glomerular basement membrane [GBM], and expansion of the mesangium) observed in rats made diabetic with streptozotocin could be reversed once diabetes was cured with islet transplantation. To verify if these findings could be translated to human diabetic patients, he carried out a prospective study on insulin-dependent diabetic patients in Minneapolis who underwent successful pancreas transplantations to cure their diabetes. At baseline, renal biopsies from those without significant renal impairment showed lesions typical of diabetic glomerulopathy. The lesions in the second biopsies performed 5 years later were not much different. However, 8 subjects underwent a third renal biopsy 10 years after they were cured of diabetes by pancreas transplantation. These biopsies showed very significant reduction in all the pathological signs of glomerular disease, and AER in these patients was satisfactory (Figure 3).

Along this line, the data on the effect of strict glycemic control in type 2 diabetic patients with high cardiovascular risk in the ADVANCE study should be kept in mind: not only did this glycemic control prevent microalbuminuria and macroalbuminuria, and perhaps protect against end-stage kidney dis-

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**Figure 3. Course of glomerular lesions in a patient cured from insulin-dependent diabetes over 10 years.**

A, A typical glomerulus from the baseline biopsy specimen, which is characterized by diffuse and nodular (Kimmelstiel-Wilson) diabetic glomerulopathy. Mesangial-matrix expansion and the palisading of mesangial nuclei around the nodular lesions are evident. B, A typical glomerulus five years after transplantation shows the persistence of the diffuse and nodular lesions. C, A typical glomerulus 10 years after transplantation, with marked resolution of diffuse and nodular mesangial lesions and more open glomerular capillary lumina.

ease, it also allowed reversal of already established microalbuminuria and macroalbuminuria, perhaps protecting against future premature death and vascular outcomes predictable from baseline AER (Figure 4).17,18 Moreover, similar findings on the effect of strict glycemic control were reported in the ACCORD12 and VADT19 studies.

Thus, high-glucose memory effects on functional and anatomical signs of diabetic vascular disease can be reversed over time.

**Legacy effect: observable for variables other than glucose?**

Posttrial effects of intervention to control particular risk factors, including abnormal lipid profiles and blood pressure, have been studied in the cardiovascular domain. For example, as WOSCOP (West Of Scotland COronary Prevention study) initially showed that primary intervention with pravastatin 40 mg per day was beneficial (compared with placebo) in terms of risk for cardiovascular death, myocardial infarction, and stroke,20 a follow-up study was implemented to examine continuation of the benefit over several years after trial cessation. Indeed, the hazard ratio was almost unchanged between groups, thereby increasing the initially observed benefit, although blood lipids regressed to similar levels in the active drug and in the placebo groups at trial’s end.21

Similar findings were reported following the HOPE study (Heart Outcomes Prevention Evaluation): 2.6 years after cessation of exposure to ramipril 10 mg per day or to placebo, benefits on risk for myocardial infarction or diabetes onset were still observable, with reductions in relative risks of 19% and 34%, respectively.22 These hazard ratios were not different from those observed in the HOPE trial.23 The follow-up period was relatively short, and the hazard ratios did not change over time.

On the other hand, the follow-up of the UKPDS blood pressure arm was disappointing in that no legacy effect was found from the use of intensified blood pressure treatment.15 A reduced risk for microvascular disease persisted for only 3-4 years, but all other risks were similar for the arms after 1-2 years.

Thus it seems from these studies that a memory (or legacy) effect is more easily detectable for interventions aiming to control blood glucose than those targeting blood lipids or blood pressure. However, several factors seem important: first, the nature of the studied variable; second, the nature of the studied outcome; and third, the duration of observation. Regarding nature of the studied variable, let’s look at blood pressure, for example. This is a hemodynamic variable that can have an impact in the short term (as illustrated by the brilliant and, at that time, unexpected effects of intensified blood pres-

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**Figure 4. Impact of updated albumin excretion rates and of glomerular filtration rates on risk for adverse vascular outcomes during the ADVANCE study.**

**Abbreviations:** ADVANCE, Action in Diabetes and Vascular disease: Preterax and Diamicron MR Controlled Evaluation; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; SBP, systolic blood pressure; UACR, urinary albumin-to-creatinine ratio.


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The legacy effect in type 2 diabetes: fact or fiction? – Marre
sure lowering on microvascular outcomes in the UKPDS, but whose benefit can vanish early after intervention cessation. This should be kept in mind when considering the HOPE-TOO study (HOPE-The Ongoing Outcomes), whose duration was relatively (2.5 years) short, compared with that of the UKPDS follow-up study. As regards nature of the studied outcome, one should consider that the legacy effect may be due to alterations in anatomy, not only alteration in functional outcomes. This is illustrated by the data on renal outcomes in type 1 diabetic patients. Regarding the duration of observation, as described above, several years of strict glycemic control may be necessary to allow regression of anatomical damage (and reduction of GBM width or mesangial expansion in remnant glomeruli does not mean revival of those occluded by sclerosis), while some weeks or days of reduction in high blood pressure suffice to reduce AER. Thus, the longer the duration of the initial intervention, the more plausible a legacy effect; and the longer the posttrial observation, the more reliable the posttrial data.

It is highly plausible that intervention against high glucose affects both the biochemical and the hemodynamic components of vascular disease, referring to now old hypotheses both on the biochemical and hemodynamic origins of diabetic microangiopathy. Both these components can have very positive interactions. Possible mechanisms behind the observed effects

Soon after the first reports of a possible negative effect of short-term transition from uncontrolled hyperglycemia to strict glycemic control in patients with insulin-dependent diabetes and background retinopathy, an experimental model was set up to examine this phenomenon. The studies were conducted on the retinas of dogs rendered diabetic with alloxan and followed over a 5-year period.

The first group was left with uncontrolled diabetes, and retinas displayed typical, severe, diabetic retinopathy at study’s end. The second group was treated intensively for diabetes, and it displayed no, or minimal diabetic retinopathy. The third group was left uncontrolled (as was the first one) for the first 2.5 years, and then treated as was the second group; at study end, the retinas were almost as severely damaged as in the first group. These data illustrated well a role for primary prevention of diabetic complications by strict glycemic control from the earliest time after diabetes diagnosis, and the difficulty to reverse established lesions, even those at early stages.

However, the biochemical mechanisms behind the memory phenomenon remained to be studied. A comprehensive review of the literature was produced by Ceriello et al. The first biochemical data were reported on the composition of the basement membrane: components such as collagen (hyperglycemia favoring production of collagen IV and fibronectin) which may make it more permeable with functional changes that favor establishment of microvascular disease. Furthermore, changes in glycation may alter the electrical charges of proteins, contributing further to alterations in their properties and/or functions. Half-life of these components may be especially long, and this may contribute to the formation of lesions, accounting in part for the glucose memory phenomenon. Many proteins are sensitive to glycation (eg, hemoglobin), and as the half-life of such products is considerably variable, they contribute to functional and structural consequences in many organs in the long term. Indeed, the role of advanced glycation end products (AGEs) in the constitution and permanence of microvascular diseases has been studied in depth.

Brownlee and his group demonstrated the biochemical links between hyperglycemia resulting in excessive production of superoxide anions ($O_2^-$) and the development of diabetic complications through several pathways: increased polyol pathway flux, increased AGE formation, activation of protein ki-
The impact of moderate hyperglycemia on structure and function of the organism is illustrated by the fate of offspring of diabetic mothers. Increased risk for renal diseases in offspring of type 1 diabetic mothers is different from that in offspring of type 1 diabetic fathers. Recently obtained preliminary data suggest that the methylation profile of the genome in offspring of type 1 diabetic mothers is different from that in offspring of type 1 diabetic fathers. This finding supports the idea that exposure to moderate hyperglycemia can alter function and perhaps structure in the very long term, and that periods of hyperglycemia affect the genome, leaving an imprint on the future of organisms, especially regarding vasculature.

Perspectives and conclusion
Just how periods of hyperglycemia impact on the vascular fate of diabetic subjects remains to be elucidated. Mechanisms may include hemodynamic anomalies or be more biochemical in nature. Interestingly, the pathways through which they affect vessel structure in the long term may be very similar: the processes of inflammation and, later on, sclerosis that are activated by diabetes and hypertension are the same and include mitogen-activated protein (MAP) kinase and nuclear factor κB (NF-κB) pathways. Thus, the duration of exposure is of utmost importance. Secondary interventions are probably less useful than primary interventions, though any given studied outcome may by nature be more sensitive or less sensitive to such interventions. Intuitively, alterations in structure, such as nephron loss, seem more or less irreversible. It is therefore highly recommended to set up long-term follow-up studies of outcome trials like DCCT, UKPDS, ACCORD, or ADVANCE.

To this end, the prospective ADVANCE-ON study was established to follow-up the participants of ADVANCE. Important data are expected to come from this study, and they are needed as thus far the only available follow-up study in type 2 diabetes is the UKPDS. Unfortunately, the UKPDS is out of step with the contemporary setting of diabetes care (several of the drugs tested then are no longer available, or are not used frequently). Also, today, absolute vascular risk is much lower than it was for people with type 2 diabetes in the 1980s. The UKPDS was a primary intervention study, conducted in patients diagnosed with type 2 diabetes. Thus, data on secondary interventions against hyperglycemia are greatly needed, and ADVANCE-ON is perfectly sized for this purpose. Other contemporary posttrial studies are currently underway, in particular ACCORD-ON (see above), and ORIGINALE (ORIGIN And Legacy Effects), the follow-up of the recently published ORIGIN study (Outcome Reduction with an Initial Glargine Intervention). It is important to properly document the long-term impact of various strategies in diabetes, since it is a lifelong condition, and to document the efficacy and safety of the drugs used in these settings.

References

The legacy effect in type 2 diabetes: fact or fiction? – Marié

Keywords: advanced glycation end product; epigenetics; hyperglycemia; legacy effect; memory effect; retinopathy; type 2 diabetes

L’EFFET HÉRITAGE DANS LE DIABÈTE DE TYPE 2 : RÉALITÉ OU FICTION ?

Le diabète est une pathologie qui dure toute une vie ; il est donc extrêmement important de comprendre quel est « l’héritage » sur un plan vasculaire des actions menées à long terme. Des études d’intervention conduites, il y a de nombreuses années, sur la maladie rétinienne diabétique dans le diabète de type 1 ont donné naissance au concept d’« effet de mémoire » dans le diabète non contrôlé. Il est biologiquement plausible, en effet, qu’il y ait un effet à long terme d’une glycémie élevée sur les fonctions et la structure des vaisseaux, avec un impact sur l’évolution de la maladie. Comme l’indique l’étude UKPDS (United Kingdom Prospective Diabetes Study), agir sur le contrôle glycémique peut en particulier réduire, à long terme, le risque de décès prématuré. Cet effet d’héritage ne s’applique d’ail- leurs pas seulement à l’hyperglycémie, mais aussi à d’autres facteurs de risque vasculaires, comme l’hypertension et un profil lipidique anormal. De nombreux facteurs pouvant entrer en jeu au cours d’une vie, il est important de mettre en place des études prospectives de suivi de patients dans le cadre d’études cliniques vasculaires à grande échelle. La durée du suivi doit cependant être assez longue pour être cliniquement significative. C’est dans cette perspective qu’a été mise en place l’étude ADVANCE-ON (Action in Diabetes and Vascular disease : PrerAx and DiamicroN MR Controlled Evaluation posttrial ObservatioNal study) qui doit permettre d’obtenir des données im- portantes de suivi dans le cadre de la prise en charge actuelle du diabète de type 2.
ADVANCE-ON [Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation posttrial ObservatioNal study] aims to determine the posttrial effects of the two interventions studied in ADVANCE: (i) the glucose-lowering intervention (intensive gliclazide MR-based versus standard guideline-based therapy) and (ii) the blood pressure-lowering intervention (routine therapy with perindopril-indapamide versus placebo) in individuals with type 2 diabetes. ADVANCE-ON will clarify and quantify the long-term (often referred to as legacy) effects of these two interventions in a broader population of patients at high risk of cardiovascular events, from high- and low-to-middle- income countries, and in the setting of comprehensive risk factor management. The conclusions of this follow-up study are expected to have profound clinical implications for the care of patients with type 2 diabetes around the world.


Rationale for ADVANCE-ON

◆ Intensive glucose lowering

Epidemiological studies have previously demonstrated an important relationship between the level of glycemic control and risks of macrovascular and microvascular complications in people with type 2 diabetes. In patients with newly diagnosed type 2 diabetes in the UKPDS (United Kingdom Prospective Diabetes Study), tight glucose control (achieved HbA1c 7%) led to significant reductions in the risk of microvascular events, a trend toward a reduction in myocardial infarction, and significant reduction in macrovascular events in the subgroup of patients allocated to metformin treatment. These data suggested that a strategy to intensively lower glucose in all patients with type 2 diabetes might reduce such outcomes. However, a reduction in macrovascular events has not been confirmed in recent large-scale clinical trials with intensive glucose lowering (achieved HbA1c range: 6.4% to 6.9%) in patients of long-standing type 2 diabetes (ADVANCE, ACCORD, VADT, Veterans Affairs Diabetes Trial).

In the glucose-control comparison of the ADVANCE trial after a mean follow-up period of 4.8 years, intensive glucose lowering based on gliclazide MR (modified release) and other glucose-lowering therapies added to achieve a mean HbA1c of 6.5% (versus 7.3% in the standard glucose control group) was associated with a reduced
risk of major macrovascular or microvascular events (hazard ratio [HR] 0.90; 95% confidence interval [CI], 0.82-0.98; P=0.01) (Figure 1A).

There was a separate reduction in major microvascular events (HR 0.86; 95% CI, 0.76-0.98; P=0.02) (Figure 1A), primarily due to a reduction in the incidence of nephropathy (HR 0.79; 95% CI, 0.66-0.93; P=0.006) with no significant effect on retinopathy. In addition, the risks of major macrovascular events, death from cardiovascular cause, and death from any cause were not significantly reduced (macrovascular events: 0.94; 95% CI, 0.84-1.06; P=0.32; death from cardiovascular cause: 0.88; 95% CI, 0.74-1.04; P=0.12; death from any cause: 0.93; 95% CI, 0.83-1.06; P=0.28) (Figure 1A and 1B).

For each of these outcomes, the 95% CIs of the point estimate included a HR consistent with modest, but potentially important clinical benefits.

In contrast, the ACCORD trial and the VADT reported no significant effects of intensive versus standard glucose control on macrovascular events (ACCORD and VADT) or microvascular events (VADT). In fact, the ACCORD trial, which targeted an HbA1c level of less than 6% and was conducted in a different population in North America, reported an increase in the risk of mortality with intensive versus standard glucose control and questioned the safety of intensive glucose lowering in older patients with diabetes of longer duration and with existing cardiovascular complications.³

**Long-term posttrial effects of intensive glucose lowering**

The DCCT/EDIC (Diabetes Intervention and Complications Trial/Epidemiology of Diabetes Interventions and Complications) study in patients with type 1 diabetes and no history of cardiovascular disease, hypertension, or hypercholesterolemia was the first to report the long-term beneficial effects of intensive glucose control on a range of vascular outcomes in the EDIC study.⁴ In this posttrial observational study, patients formerly assigned to intensive insulin therapy as compared with those assigned to conventional insulin therapy had a lower risk of macrovascular events as well as a sustained benefit as regards microvascular complications beyond the period of randomized treatment. This was achieved despite loss of between-group differences in glycemic control as patients in the conventional insulin therapy group were offered intensive insulin therapy for the duration of the posttrial observation period. Intensive insulin therapy was also associated with a

---

**Table 1. Effects of intensive glucose lowering with a gliclazide MR-based regimen on A) major macrovascular events, major microvascular events, and B) death.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive (n=5571)</th>
<th>Standard (n=5569)</th>
<th>Favors intensive</th>
<th>Favors standard</th>
<th>Relative risk reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Combined macro+micro</strong></td>
<td>1009</td>
<td>1116</td>
<td></td>
<td></td>
<td>10% (2 to 18)</td>
</tr>
<tr>
<td>Macrovascular</td>
<td>557</td>
<td>590</td>
<td></td>
<td></td>
<td>6% (-6 to 16)</td>
</tr>
<tr>
<td>Microvascular</td>
<td>526</td>
<td>605</td>
<td></td>
<td></td>
<td>14% (3 to 23)</td>
</tr>
<tr>
<td><strong>All deaths</strong></td>
<td>498</td>
<td>533</td>
<td></td>
<td></td>
<td>7% (-6 to 17)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>253</td>
<td>289</td>
<td></td>
<td></td>
<td>12% (-4 to 26)</td>
</tr>
<tr>
<td>Noncardiovascular death</td>
<td>245</td>
<td>244</td>
<td></td>
<td></td>
<td>0% (-20 to 16)</td>
</tr>
</tbody>
</table>

**Figure 1. Effects of intensive glucose lowering with a gliclazide MR-based regimen on A) major macrovascular events, major microvascular events, and B) death.**

reduced risk of incident hypertension during posttrial follow-up. These long-term benefits were ascribed to a “metabolic memory” effect, introducing the paradigm of the legacy effect of intensive glucose lowering.

More recently, the postintervention follow-up of the UKPDS also 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. In patients formerly assigned to intensive therapy (either sulfonylurea or insulin) compared with those formerly assigned to conventional therapy (diet alone), the reduced risk of microvascular events was maintained and a reduced risk of death from any cause and of myocardial infarction emerged with posttrial follow-up. This was achieved despite an early loss of between-group differences in glycemic control as no attempt was made to continue previously assigned therapies.

The mechanisms responsible for the legacy effect of intensive glucose lowering remain unclear. Some postulate that the long-term vascular effects of hyperglycemia may be mediated by accumulation of advanced glycation end products in the vasculature. It is therefore speculated that in the UKPDS and the DCCT/EDIC studies the earlier periods of tighter glucose control resulted in less accumulation of advanced glycation end products and emergent long-term protection from cardiovascular disease. Alternatively, the earlier tight glucose control may have reduced the development of microvascular-renal disease, a well-recognized risk factor for cardiovascular disease. Such a reduction in microvascular renal disease has previously been reported by the DCCT and the UKPDS. However, it remains uncertain as to whether any persisting or emerging long-term benefits of prior intensive glucose control will be observed in patients such as those in ADVANCE, which in comparison with those in the UKPDS were enrolled from a diverse range of countries from around the world, had longer disease duration with a mean of 8.3 years at baseline, and prevalent macrovascular disease at study entry in about one-third of the patients.

Blood pressure lowering
Among patients with type 2 diabetes, blood pressure is a particularly important determinant of cardiovascular disease risk. As reported by previous studies, this relationship is continuous and of similar strength among those with or without diabetes. In the UKPDS, systolic blood pressure levels were linearly associated with the risks of myocardial infarction and microvascular events. Additionally, in the Prospective Studies Collaboration, the association between systolic blood pressure and death was age dependent in those with diabetes with greater risks observed at younger age. A number of randomized clinical trials have previously demonstrated the cardiovascular benefits of treating hypertensive patients who have type 2 diabetes. In a meta-analysis of blood pressure-lowering therapy, the effects of treatment were similar among those with and those without diabetes. Recently, the ADVANCE trial has extended these findings by demonstrating the benefits of routine blood pressure lowering, irrespective of initial blood pressure levels, in a group of patients with established type 2 diabetes and who were at high vascular risk and receiving comprehensive preventive medical care.

In the blood pressure-lowering comparison of the ADVANCE trial after a mean follow-up period of 4.3 years, routine treatment with perindopril-indapamide versus placebo resulted in a mean reduction in systolic and diastolic blood pressure of 5.6 mm Hg and 2.2 mm Hg, respectively, and was associated with a reduced risk of major macrovascular or microvascular events (HR 0.91; 95% CI, 0.83-1.00; P=0.04). The separate reductions in macrovascular and microvascular events were similar, but not independently significant (macrovascular: 0.92; 95% CI, 0.81-1.04; P=0.16; microvascular: 0.91; 95% CI, 0.80-1.04; P=0.16) (Figure 2). The risk of death from any cause was reduced by 14% (HR 0.86; 95% CI, 0.75-0.98; P=0.03) and the risk of death from cardiovascular disease was reduced by 18% (HR 0.82; 95% CI, 0.68-0.98; P=0.03). There were also significant reductions in total coronary (HR 0.86; 95% CI, 0.76-0.98; P=0.02) and total renal events (HR 0.79; 95% CI, 0.73-0.85; P<0.0001). The reduction in renal events was largely attributable to a significant reduction in the development of microalbuminuria. Moreover,
the benefits observed appeared independent of ancillary treatments at baseline and of the presence or absence of hypertension at study entry.

Long-term posttrial effects of blood pressure lowering

Although the vascular benefits of intensively treating blood pressure in type 2 diabetes are widely accepted, persistent posttrial effects continue to be debated. In the 10-year posttrial observational follow-up of the blood pressure–lowering arm of the UKPDS, the benefits of tight blood pressure control on death, stroke, and microvascular disease were not maintained with early loss of between-group differences in blood pressure. This was attributed to the rapid “on and off effects” of blood pressure treatment as well as the drop in blood pressure levels observed in the less-tight control group during follow-up. Yet the significantly worse glycemic control in the tight versus less-tight blood pressure control group may have masked a longer-term effect. In contrast, the HOPE-TOO (Heart Outcomes Prevention Evaluation–The Ongoing Outcomes) study extension, which included patients with vascular disease and/or diabetes, demonstrated several years of maintained benefits of immediate as compared with delayed postrandomization open-label treatment of elevated blood pressure. Moreover, the relative risk reductions achieved with additional follow-up could only be explained by former allocation to active treatment, as the rate of cardiovascular events in those assigned to active treatment was similar to those assigned placebo. Whether these benefits would persist with the longer period of posttrial follow-up proposed by ADVANCE-ON (ADVANCE posttrial ObservatioNal study) remains to be seen.

ADVANCE-ON: progress

The last visits in the ADVANCE trial were completed at the end of January 2008. Phase 1 of the study will follow participants for up to 6 years after completion of randomized intervention (funded) and phase 2 will follow participants for up to 10 years (subject to funding).

<table>
<thead>
<tr>
<th></th>
<th>ADVANCE trial n=11140</th>
<th>ADVANCE-ON study n=8194</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>65.8 (6.4)</td>
<td>65.5 (6.2)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>4733 (42.5)</td>
<td>3538 (43.2)</td>
</tr>
<tr>
<td>Age when diabetes first diagnosed (years), mean (SD)</td>
<td>57.8 (8.7)</td>
<td>57.9 (8.5)</td>
</tr>
<tr>
<td>Prior vascular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of major macrovascular disease, n (%)</td>
<td>3590 (32.2)</td>
<td>2459 (30.0)</td>
</tr>
<tr>
<td>History of myocardial infarction, n (%)</td>
<td>1334 (12.0)</td>
<td>810 (9.9)</td>
</tr>
<tr>
<td>History of stroke, n (%)</td>
<td>1023 (9.2)</td>
<td>742 (9.1)</td>
</tr>
<tr>
<td>History of major microvascular disease, n (%)</td>
<td>1155 (10.4)</td>
<td>773 (9.4)</td>
</tr>
<tr>
<td>History of macroalbuminuria, n (%)</td>
<td>404 (3.6)</td>
<td>250 (3.1)</td>
</tr>
<tr>
<td>History of microvascular eye disease, n (%)</td>
<td>795 (7.1)</td>
<td>547 (6.7)</td>
</tr>
<tr>
<td>Blood glucose control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c concentration (%), median (IQR)</td>
<td>7.2 (6.5, 8.2)</td>
<td>7.2 (6.5, 8.2)</td>
</tr>
<tr>
<td>HbA1c concentration (%), mean (SD)</td>
<td>7.5 (1.6)</td>
<td>7.5 (1.5)</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/L), mean (SD)</td>
<td>8.5 (2.8)</td>
<td>8.5 (2.7)</td>
</tr>
<tr>
<td>Other major risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg), mean (SD)</td>
<td>145.0 (21.5)</td>
<td>143.9 (21.2)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg), mean (SD)</td>
<td>80.6 (10.9)</td>
<td>80.2 (10.7)</td>
</tr>
<tr>
<td>History of currently treated hypertension, n (%)</td>
<td>7655 (68.7)</td>
<td>5345 (65.2)</td>
</tr>
<tr>
<td>Serum HDL cholesterol (mmol/L), mean (SD)</td>
<td>1.3 (0.4)</td>
<td>1.3 (0.4)</td>
</tr>
<tr>
<td>Urinary albumin:creatinine ratio (ug/mg), mean (SD)</td>
<td>52.5 (115)</td>
<td>48.3 (107)</td>
</tr>
<tr>
<td>Urinary albumin:creatinine ratio (ug/mg), median (IQR)</td>
<td>15.0 (7.1, 39.8)</td>
<td>14.7 (7.1, 37.0)</td>
</tr>
<tr>
<td>Microalbuminuria, n (%)</td>
<td>2857 (25.6)</td>
<td>2090 (25.5)</td>
</tr>
<tr>
<td>Serum creatinine (umol/L), mean (SD)</td>
<td>86.5 (25.4)</td>
<td>84.6 (22.4)</td>
</tr>
<tr>
<td>Body mass index (kg/m2), mean (SD)</td>
<td>28.3 (5.2)</td>
<td>28.1 (5.2)</td>
</tr>
<tr>
<td>Waist circumference (cm), mean (SD)</td>
<td>98.5 (13.1)</td>
<td>97.4 (13.2)</td>
</tr>
</tbody>
</table>

**Table I. Comparison of the baseline participant characteristics in ADVANCE and ADVANCE-ON.**

**Abbreviations:**

ADVANCE, Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation. ADVANCE-ON, ADVANCE posttrial ObservatioNal study; HbA1c, glycated hemoglobin; IQR, interquartile range; n, number; SD, standard deviation.
All 10,063 surviving ADVANCE trial patients who returned to the care of their usual physicians after ceasing the randomized interventions were invited to participate in ADVANCE-ON. A random sample of patients was selected for repeat measurement of HbA1c and blood pressure levels.

By mid-May 2012, 8194 patients (mean age 76 years, 43% female) had completed the first posttrial visit (22% Australasia, 38% China, 4% Canada, 16% Continental Europe, and 20% Northern Europe). Of these patients, 622 had died and 1413 had provided repeat HbA1c and blood pressure measurements. A comparison of the baseline characteristics of the ADVANCE and ADVANCE-ON participants is provided in Table I.

At that time, the mean HbA1c levels of the original intensive and standard glucose control groups were 7.25% and 7.30%, respectively, and the mean blood pressure level in both the original perindopril-indapamide and placebo groups was 137/75 mm Hg. While treatment with glucose-lowering drugs had converged, 36% of those in the original intensive glucose control group were still taking insulin compared with 31% in the standard group.

Conclusions
The ADVANCE-ON cohort is representative of the original ADVANCE population. As expected, early after completion of the ADVANCE trial and cessation of the randomized interventions, the patterns of glucose and blood pressure control in the treatment groups converged. Recruitment and data collection are ongoing to ensure all posttrial patient outcomes are captured.

Acknowledgements: ADVANCE-ON is partially funded by an unrestricted educational grant from Servier International and a project grant from the National Health and Medical Research Council of Australia (NHMRC) (ID 1003967). The study was initiated and designed by the investigators, independently of Servier and the NHMRC, and the data will be collected, analyzed and published independently of Servier.

References

Keywords: ADVANCE-ON; blood pressure lowering; HbA1c; intensive glucose lowering; long-term posttrial effect; type 2 diabetes
L’étude ADVANCE-ON (Action in Diabetes and Vascular disease PreterAx and Diamicron MR Controlled Evaluation posttrial ObservatioNal study) : où en sommes-nous ?

Le but de l’étude ADVANCE-ON (Action in Diabetes and Vascular disease : PreterAx and Diamicron MR Controlled Evaluation posttrial ObservatioNal study) est de déterminer les effets à long terme des deux traitements étudiés dans ADVANCE : (1) l’abaissement de la glycémie (traitement intensif par le gliclazide LM versus traitement standard) et (2) l’abaissement de la pression artérielle (traitement de routine avec le périndopril-indapamide versus placebo) chez des diabétiques de type 2. L’étude ADVANCE-ON va permettre d’éclaircir et quantifier les effets à long terme (souvent appelés « héritage ») de ces deux expériences dans une plus large population comprenant des patients à haut risque d’événements cardiovasculaires, issus de pays à revenus élevés et de pays à revenus faibles à moyens, et dans le cadre d’une prise en charge globale des facteurs de risque. Les conclusions de cette étude de suivi devraient avoir des implications cliniques importantes pour le traitement des diabétiques de type 2 au niveau mondial.
The G.B. Morgagni Prizes were instituted in 1984 by a group of postdoctoral researchers working at the Medical School of the University of Padova (Italy). Named to honor Giovanni Battista Morgagni, the Italian anatomist called the founder of pathologic anatomy (1682-1771), the prizes were set up to promote research in the field of metabolism.

The prizes, consisting of one Morgagni Medal (Gold Medal and € 20 000) and two Young Investigator Awards (Silver Medal and € 8 000), are conferred every 2 years for outstanding achievements in the field of metabolism.

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Applications should be sent to Professor Gaetano Crepaldi, The G.B. Morgagni Prizes Committee, Centro Studio per l’Invecchiamento-C.N.R., Via Giustiniani 2, 35128 Padova, Italy

E-mail: crepaldi.metabolism@unipd.it
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**Aim and grant:** This grant of **€40 000** is given every two years and is aimed specifically at encouraging young scientists to carry out high-quality research in the field of osteoporosis.

**Who may apply:** Young scientists up to 40 years of age.

**How to apply:** Instructions available on the IOF Web site: [www.iofbonehealth.org](http://www.iofbonehealth.org) and [www.servier.com](http://www.servier.com)

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**Aim and grant:** Servier is a partner of the Union Internationale de Phlébologie (UIP). Every 2 years, the UIP/Servier Research Fellowship provides a **€25 000** grant for a 2-year research project consisting of original clinical or basic research in the areas of phlebology and lymphology, including the following topics: anatomy, physiology, pathophysiology, diagnostic methods, and clinical research.

**Who may apply:** Candidates less than 45 years old and belonging to a National Society affiliated with the UIP.

**How to apply:** Instructions are available on the Servier Web site: [www.servier.com](http://www.servier.com), together with the electronic application file.

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**Aim and grant:** A grant of **€40 000** presented every year by the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) and the International Osteoporosis Foundation (IOF), with the exclusive support of Servier.

**Who may apply:** Any individual with outstanding and major scientific contributions in the study of bone and mineral diseases.

**How to apply:** Instructions are available on the ESCEO Web site: [www.esceo.org](http://www.esceo.org); on the IOF Web site: [iofbonehealth.org](http://iofbonehealth.org); or on the Servier Web site: [www.servier.com](http://www.servier.com)

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**Aim and grant:** A Master’s offering postgraduate specialization in Affective Neuroscience for clinicians and researchers, which includes an intensive residential session taught by leading neuroscientists. It is part of a joint Master’s program organized by Maastricht University and Florence University.

**Who may apply:** Graduates with an MSc in Psychology, Behavioral Sciences, Psychiatry, or a related discipline, or an MD.

**How to apply:** Instructions are available at: [http://affect-neuroscience.org](http://affect-neuroscience.org)

For further information and application deadlines, please visit our Web site: [www.servier.com](http://www.servier.com)
THE QUESTION

Despite discrepancies in HbA1c target recommendations, there is a general perception that a target of 7% is somehow good enough for all type 2 diabetic patients. Indeed, conflicting findings from trials targeting levels of 6.5% or less make choosing a lower target controversial, eg, one shows an increase in cardiovascular death, the other a reduction. So, which evidence-based HbA1c target should we choose? If one target isn’t suitable for all, should the target be individualized to each patient?

HbA1c targets: does one size fit all or should they be tailored to individual patients?

1. B. Bauduceau, France
2. F. Carrilho, Portugal
3. L. Czupryniak, Poland
4. N. Ghannam, Saudi Arabia
5. L. Litwak, Argentina
6. B. Mankovsky, Ukraine
7. M. Mota, D. Protasiewicz, S. G. Popa, Romania
8. A. Orabi, Egypt
9. U. Phadke, India
10. M. V. Shestakova, Russia
11. L. Smircic-Duvnjak, Croatia
12. B. Tschiedel, Brazil
13. Z. Visockiene, Lithuania
The discrepancies between different international recommendations clearly show that determining an optimal glycated hemoglobin (HbA1c) target is not an easy task. However, the majority of these recommendations indicate that an HbA1c target of 7% is good enough for all diabetic patients.

In diabetology, the year 2008 was replete with learning experiences and suspense. Past studies, the UKPDS (United Kingdom Prospective Diabetes Study) in type 2 diabetic patients and the DCCT (the Diabetes Control and Complications Trial) in type 1 diabetic patients, have shown that intensive treatment over a short period reduces the incidence of microvascular events and, in the long term, the incidence of macrovascular events linked to diabetes. Nevertheless, conclusions from recent analyses of ACCORD (the Action to Control Cardiovascular Risk in Diabetes study) showed increased mortality in type 2 diabetic patients that used an intensive therapy. ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation), on the other hand, showed a 12% reduction in cardiovascular death and a 21% reduction in nephropathy in such patients. And the VADT (Veterans Affairs Diabetes Trial) showed no effect. Analysis of studies published since 2008 has contributed new knowledge, especially concerning glycemic memory, to clinical practice. Consequently, we now understand the importance of earlier detection and treatment of diabetic patients through lifestyle improvements and drugs, if necessary. Thus, early treatment of diabetes and prevention of hypoglycemia should be essential components of treatment strategies.

Moreover, results from the Steno-2 study showed that control of cardiovascular risk factors dramatically improves the prognosis of type 2 diabetes. The treatment of hypertension, for example, is always useful because of the absence of tensional memory. Though management of type 2 diabetic patients requires early treatment combined with strict control of cardiovascular risk factors, this should be done without intensive methods, so as to avoid hypoglycemia. HbA1c targets should be based on many criteria, including patient characteristics and potential adverse drug events, such as hypoglycemia. Thus, there is no single HbA1c level that can be considered the optimal target for all diabetic patients.

HbA1c targets must be individualized, as is the profile of each patient, including age, history of diabetes, presence of complications, and potential risk of hypoglycemia. To summarize and to simplify, a young diabetic patient with recently discovered diabetes and without cardiovascular complications should receive intensive treatment in order to reach the target HbA1c level of 6.5%. On the other hand, much caution should be exercised for elderly or frail patients. The risk of hypoglycemia is very high for this population with cardiovascular or cerebral complications. Cognitive decline, dementia, and depression in elderly patients increase the risk of hypoglycemia, leading to poor quality of life with considerable social and economic impacts. Accordingly, the target HbA1c level must be adjusted to lie between 7.5% and 8.5%.

In conclusion, we should focus on the patient. Definition of the HbA1c target must consider all the characteristics of the particular diabetes condition, comorbid diseases, and the social situation of each patient.

References
Type 2 diabetes is a very complex disease, more so than we previously thought. Patients with type 2 diabetes treated with aggressive management of glycemic control and cardiovascular risk factors have greater benefits in regard to microvascular complications, but remain at elevated risk of cardiovascular morbidity and mortality. Type 2 diabetes is also associated with increased risk of cancer, cognitive decline, and chronic liver disease. Many clinicians are calling for a more realistic approach to treatment of patients with type 2 diabetes. They emphasize that diabetic patients are very different from one another with regard to age, duration of disease, motivation, associated comorbidities, and so on.

Glycated hemoglobin (HbA1c) is the principal target of treatment as it reflects blood glucose level and is associated with the risk of microvascular and macrovascular complications. In the UKPDS (UnitedKingdomProspectiveDiabetesStudy), intensive therapy was associated with a reduction in the risk of microvascular complications; however, reduction in myocardial infarction rates did not reach statistical significance. Nevertheless, the 10-year follow-up demonstrated statistically significant benefits in terms of cardiovascular end points and total mortality in the intensive group. Thus, macrovascular benefits emerge over time and so take longer to evaluate.

Three studies—ACCORD (Action to Control CardiOvascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation), and the VADT (Veterans Affairs Diabetes Trial)—published in 2008, with two protocols for more intensive or less intensive glycemic control, evaluated cardiovascular end points in middle-aged and older diabetic patients with high risk for cardiovascular events. ACCORD and the VADT used oral agents, insulin, and a target HbA1c of <6.0%. ADVANCE patients were treated with glimepiride targeting an HbA1c of <6.5%. None of the trials demonstrated a significant reduction in the combined cardiovascular end points. A 22% increase in total mortality, mainly attributable to cardiovascular mortality, with intensive treatment was found in ACCORD. Was hypoglycemia the cause for this high mortality rate or was it due to the higher complexity of the patients and therapies?

For clinical practice, the results of the aforementioned studies suggest that intensive glycemic treatment of diabetic patients is not good for all. The new perspective emphasizes individualized treatment objectives and targets. To decide on an HbA1c target, the clinician needs to evaluate: (i) patient attitude and cooperation; (ii) hypoglycemia and associated risks; (iii) disease duration; (iv) life expectancy; (v) associated comorbidities and established vascular complications; (vi) costs, and health care system support.

Some health care organizations evaluate the percentage of diabetic patients who achieve an HbA1c of <7.0% as a quality indicator, but such practice is inconsistent with an emphasis on individualization of the treatment of type 2 diabetic patients. The American Diabetes Association recommends an HbA1c of <7.0% for the great majority of patients in order to reduce microvascular complications. HbA1c targets of 6.0%-6.5% may be appropriate in patients with short disease duration, no vascular comorbidities, no important hypoglycemic events, and a long life expectancy. However, HbA1c targets of 7.5%-8.0% or slightly higher may be appropriate for more complicated patients with important vascular comorbidities, severe hypoglycemia, and limited life expectancy. In conclusion, we must tailor the HbA1c target to the patient.

Patient-centered care is “providing care that is respectful of and responsive to individual patient preferences, needs, and values.” Patient preferences are particularly important with regard to lifestyle choices as this defines how patients live their everyday lives. Pharmaceutical intervention can also be, to some degree, a shared-decision approach. Involvement of the patient in health care decisions enhances adherence to therapy.

References
In 2012, the answer to this question is simple: we should absolutely tailor the therapy target to every patient we treat. However, only a few years ago, the answer would have been quite the opposite: treat all diabetic subjects to one glycated hemoglobin (HbA1c) target, eg, ≤7% according to the American Diabetes Association and the European Association for the Study of Diabetes (ADA/EASD) consensus or ≤6.5% as per the International Diabetes Federation (IDF) guideline. Our view on blood glucose targets and hyperglycemia management strategies in type 2 diabetes changed thoroughly in 2008.

In 2008, the results of ACCORD (Action to Control Cardiovascular Risk in Diabetes) and the VADT (Veterans Affairs Diabetes Trial) were published, showing that targeting an HbA1c of <6.5% or <7% is beneficial only for younger patients without a history of microvascular and macrovascular complications. These data sparked many analyses and commentaries, and eventually led to publication of the extensively revised ADA/EASD position statement in April 2012.

That position statement is a milestone in the history of diabetes guidelines. It very convincingly documents why we should abandon the one-target-fits-all strategy and depicts the complexity of type 2 diabetes management. For the first time, such elements like patient motivation, hypoglycemia-associated risks, disease duration, life expectancy, presence of comorbidities and advanced vascular complications, and the availability of health care resources were strongly recommended to be taken into account while setting therapy targets. The importance of the individualization of dietary and exercise advice as well as drug regimens has also been fully justified, and various HbA1c targets have been proposed. An HbA1c of <7.0% is recommended in most patients so as to reduce the incidence of microvascular disease; more stringent targets of 6.0%-6.5% are for patients with short disease duration, long life expectancy, and no significant cardiovascular disease, providing this can be achieved without significant hypoglycemia or other adverse effects of treatment; and less stringent goals (7.5%-8.0% or even higher) are appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced complications, extensive comorbid conditions, and those in whom the target is difficult to attain despite intensive education and effective doses of multiple glucose-lowering agents. Most importantly, the position statement makes it clear that the desires and values of the patient should be considered, since the achievement of any degree of glucose control requires his or her active participation and commitment. In fact, any decided target should reflect an agreement between patient and clinician.

Therefore, a 52-year-old woman with newly diagnosed type 2 diabetes should be treated so that her blood glucose remains within the (near) normal range. Why? Simply put, in the clinic, when we see a “healthy” (without other significant health problems) type 2 diabetic, we should do our best to maintain that patient’s health and protect the cardiovascular system from being damaged by hyperglycemia in the years to follow. However, for a 75-year-old man treated 20 years for type 2 diabetes, who has a history of myocardial infarction, repeated retinal photoocoagulation and right big toe amputation, the target should be somewhere between 7% and 8%. We know today that lowering his blood glucose to achieve an HbA1c of <6.5% will not repair his vasculature or reduce his cardiovascular risk.

Tailoring HbA1c targets, leading to diversifying of glucose control regimens may be considered bad news for the medical community, as type 2 diabetes treatment will become more varied and thus complicated; however, it is great news for the patients, as we will be able to help each of them more—as different as they are—without doing (or at least doing less) harm.

References
Glycated hemoglobin (HbA1c) measurement is integral to the management of individuals with diabetes. Studies such as UKPDS (United Kingdom Prospective Diabetes Study) and ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation) have confirmed that lowering HbA1c is of great importance to achieve risk reduction for complications in patients with diabetes. The recommended target of HbA1c <7% basically comes from studies such as ADVANCE, ACCORD (Action to Control Cardiovascular Risk in Diabetes), and the VADT (Veterans Affairs Diabetes Trial). ACCORD and the VADT both showed increases in cardiovascular disease morbidity and mortality risks, therefore the International Diabetes Federation (IDF), the American Diabetes Association (ADA), and most diabetes societies generally recommended the target of HbA1c <7.0% which is less strict, but recommended to aim for a lower HbA1c in patients who are younger, who have had diabetes for a short time, and who have no cardiovascular complications. Therefore, there is a general target and there is an individualized target. This is very important, especially when addressed as early as possible, as it has been suggested that with earlier and more aggressive intervention, we are more successful in reaching the target than with conventional therapy, and the resulting benefit is known as the legacy effect.

Why should we address HbA1c levels? One reason is that the UKPDS showed a relationship between the risk of fatal myocardial infarction (MI), nonfatal MI, and risk reduction for complications with lowering of HbA1c. Other published data shows that HbA1c level is a predictor of mortality, and this increase in risk appears between the levels of 5%-6% and is obvious at an HbA1c >7.0%.

To sum up, there are three major points each clinician should keep in mind when measuring baseline HbA1c in patients with diabetes and when trying to reach an HbA1c target: (i) Is the patient already at the general target for HbA1c, i.e., <7%? If yes, is it possible and is it safe to target a lower HbA1c, i.e., <6.5%? If baseline HbA1c is not <7%, the aim should be to reach this target and then reevaluate the need for a lower HbA1c. (ii) Is it possible to target an HbA1c of <6.5% for a particular patient? (iii) Apart from HbA1c and hyperglycemia, are there other associated comorbidities that need to be addressed in order to reduce the risk of cardiovascular complications? These comorbidities may include blood pressure, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol.

Finally, the argument should not be about trying to find a particular HbA1c target that fits all patients. Even an acceptable target might be “too loose” or “too tight” for some patients. Thus, the target should be individualized, for example, we definitely need an aggressive approach targeting an HbA1c <6.5% for newly diagnosed and younger patients with no diabetes complications.

References

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Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in type 2 diabetic patients, and glycated hemoglobin (HbA1c) levels are strongly correlated with risk of microvascular and macrovascular complications, even in nondiabetic subjects.  

Convincing evidence shows that the lower HbA1c threshold for macrovascular events should be 7%, and for microvascular disease it should be 6.5%. Every 1% above this boundary is associated with a 38%, 40%, and 38% higher risk for macrovascular and microvascular events, and death, respectively. On the other hand, the UKPDS (United Kingdom Prospective Diabetes Study) showed that every 1% decrease in HbA1c levels was associated with a 14% lower risk of myocardial infarction, 37% less microvascular disease, and a 14% lower risk of death. Based on this, HbA1c targets reflecting adequate metabolic (glycemic) control should be accepted—for all the patients—at <6.5% to avoid these complications.

Three major studies were designed to evaluate the impact of attaining “euglycemia” (ACCORD [Action to Control Cardiovascular Risk in Diabetics] or near-euglycemia) [ADVANCE [Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation] and the VADT [Veterans Affairs Diabetes Trial]) on macrovascular outcomes and mortality in type 2 diabetic patients. Collectively, the results of these trials showed some benefits from intensive glucose control, such as reductions in nonfatal myocardial infarction, blood pressure, and progression of microalbuminuria, but none changed (quickly) since 2006, introducing a patient-centered approach. Most-intensive approaches (HbA1c <6%-6.5%) should be considered in pregnancy and in highly motivated, compliant young patients with adequate resources, low risk of hypoglycemia, short duration of the disease, long life expectancy, and absence of microvascular disease, CVD, and comorbidities. On the other hand, less-intensive treatments (HbA1c >7.5%-8%) should be offered to older type 2 diabetic patients that are less motivated, noncompliant, who have inadequate resources, high risk of hypoglycemia, long duration of the disease, shorter life expectancy, advanced microvascular complications, presence of CVD, and multiple or severe coexisting conditions. Indeed, for patients over 70 years, the proposed range for HbA1c is between 7.5% and 8.5%.

For the remaining type 2 diabetic patients, we should consider the universally accepted target of a mean HbA1c of 7%. We must tailor therapeutic goals for each patient thusly: first, determine the HbA1c target together with the other therapeutic targets (hypertension, lipids, weight, etc); second, build a personalized treatment with combined goals (glycemic, blood pressure, lipids, weight); and third, avoid side effects and elevated costs.

**References**


**Controversial Question**

HbA1c targets does one size fit all?
The level of glycated hemoglobin (HbA1c) is the most important parameter characterizing metabolic control in patients with type 1 and type 2 diabetes mellitus and is emphasized by all guidelines on the management of these patients. However, there is an ongoing discussion about what level of HbA1c should be achieved and whether this goal is the same for all patients with diabetes.

Most respected authorities (eg, American Diabetes Association [ADA], 2012; International Diabetes Federation [IDF], 2011) advocate an HbA1c target below 7%.1,2 This target is based on strong epidemiological data which showed a linear increase in microvascular and macrovascular risk if HbA1c levels exceed 7%, and a much more gradual increase in risk at HbA1c levels below 7%. In ADVANCE (Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation), a 1% increase in HbA1c was associated with increased risks of microvascular complications (26%), macrovascular complications (22%), total mortality (22%), and cardiovascular mortality (25%).3

From a clinical standpoint, it is very important to know whether we should aim for lower HbA1c levels. Findings from ADVANCE and ACCORD (Action to Control Cardiovascular Risk in Diabetes) make choosing a lower target controversial. While ACCORD showed a 22% increase in total mortality and a 35% increase in cardiovascular death in intensively treated diabetic patients,4 ADVANCE showed a 10% reduction in combined microvascular and macrovascular end points and a 21% reduction in nephropathy in intensively treated patients. The HbA1c levels achieved were similar in the intensive arms of these 2 trials: 6.4% and 6.5%, respectively. However, even in ACCORD, not all results were negative. The intensive control of blood glucose was beneficial for the reduction of primary end points in diabetic patients with basal HbA1c levels below 8% and no history of cardiovascular disease. Therefore, these landmark clinical trials justify the individualized approach to the treatment of patients with type 2 diabetes. Moreover, the recent position statement (April 2012) of the ADA and the European Association for the Study of Diabetes (EASD) highlights the importance of patient-oriented treatment. For example, in type 2 diabetic patients with a long life expectancy and no history of cardiovascular disease, who are newly diagnosed or at least have had diabetes only for a short duration (less than 5 years), we should aim for HbA1c levels below 6.5% toward normoglycemia, so as to prevent development of microvascular complications and significantly reduce the risk of macrovascular complications. However, we must consider whether this HbA1c level can be achieved without significantly increasing the risk of hypoglycemia. Even in such a relatively healthy group of subjects, if treatment to achieve normoglycemia leads to frequent and severe hypoglycemia, the HbA1c goal should be loosened to 7.0%. Social issues, eg, patient’s occupation and marital status, should also be considered. If, due to the social situation, the risk of hypoglycemia is unacceptable, the target should be loosened.

On the other hand, in type 2 diabetic patients with a short life expectancy, history of cardiovascular disease, significant risk of hypoglycemia, and high medical and social risk of hypoglycemic episodes, the HbA1c target should be higher, with an upper threshold of 7.5% or in some cases even higher, below 8%. However, one should realize that increasing the target level of HbA1c is associated with higher risk of diabetic complications, especially retinopathy and nephropathy, and such loosening of glycemic control is a compromise due to difficult circumstances in a specific patient profile. We believe that the results of ongoing trials such as ADVANCE-ON (ADVANCE posttrial ObservatioNal study) will shed further light on the benefits and long-term safety of strict metabolic control.

References
Glycated hemoglobin (HbA1c) was introduced into clinical use in the 1980s and nowadays has become a cornerstone of clinical practice. Many organizations—AACE (American Association of Clinical Endocrinologists), ADA (American Diabetes Association), EASD (European Association for the Study of Diabetes), IDF (International Diabetes Federation), and UK NICE (National Institute for Health and Clinical Excellence)—currently advocate a target level for HbA1c of 6.5%-7%. They also agree that the therapeutic targets should be individualized.

As a consequence of the failure of the intensive treatment arm of the ACCORD study (Action to Control Cardiovascular Risk in Diabetes), the ACC (American College of Cardiology), ADA, and AHA (American Heart Association) issued a joint position statement recommending that the general target for HbA1c should be <7%, but for some patients they recommended individualized glycemic targets.1 Lowering HbA1c levels to below or around 7% has been shown to reduce microvascular complications of diabetes and, if implemented soon after the diagnosis of diabetes mellitus, is associated with long-term reduction in macrovascular disease.2,3 Patients with limited life expectancy, extensive comorbid conditions, long-standing diabetes, advanced microvascular and macrovascular complications, a history of severe hypoglycemia, or inappropriate glucose monitoring possibilities, should have less stringent HbA1c goals.

The DCCT (Diabetes Control and Complications Trial), the Kumamoto study (Kumamoto Study on Optimal Diabetes Control in Type 2 Diabetic Patients), the UKPDS (United Kingdom Prospective Diabetes Study), the VADT (Veterans Affairs Diabetes Trial), ACCORD, and ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation) proved that glycemic control is fundamental in the management of diabetes. Recently, the need for individualization has gained interest because of the results of the glycemic intervention in the ACCORD study.

In the group treated intensively, with an HbA1c target of <6%, mortality increased by 22%, requiring premature discontinuation of the study.1 There are fears that increased mortality could be the result of an HbA1c level that is lowered too much and/or decreasing too rapidly. Although the number of hypoglycemia events was higher in the intensively managed group, an association with higher risk of mortality was not proven.

The ADVANCE study analyzed the intensive treatment group (target HbA1c =6.5%) versus the standard treatment group in patients with more than 55 years of age, a mean HbA1c of 7.5%, having type 2 diabetes, and a history of major microvascular and macrovascular complications or at least another cardiovascular (CV) risk factor. Although patients in the intensive control group suffered more severe hypoglycemia episodes (2.7% vs 1.5% of those in the standard control group) and more weight gain (+0.1 kg vs -0.8 kg for those in the standard control group), there seemed to be a 22% reduction in all-cause mortality, and a 25% reduced CV mortality for every 1% reduction in HbA1c.

The VADT analyzed CV events in an intensive glycemic control group (HbA1c goal =6.0%) vs a standard glycemic control group (HbA1c goal =8.0%-9.0%). No difference in mortality was registered,1 but one should note that the hypoglycemic events were three to four times higher in the intensive control group than in the standard control group.

The UKPDS—a prospective, randomized, controlled trial of intensive vs standard glycemic control in patients with recent type 2 diabetes—showed that improved glycemic control is associated with significantly decreased rates of microvascular complications. The DCCT and the Kumamoto study reported the same benefits from improved glycemic control.

In conclusion, we the clinicians should keep in mind the key words for this approach: “maximizing benefit while minimizing risks.”

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References
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n the normal 120-day life span of the red blood cell, glucose reacts with hemoglobin, forming glycated hemoglobin (HbA1c). Once glycated, it remains that way. A buildup of HbA1c, therefore, reflects the average level of glucose to which the red cell has been exposed. In general, the reference range (that found in healthy subjects) is about 4%-5.9%. 1

As HbA1c is the laboratory measure that captures long-term blood glucose exposure, it should provide a better marker for the presence and severity of the disease than single measures of glucose concentration. The correlation between HbA1c levels and complications has been proven by many controlled trials in type 1 and type 2 diabetes; most importantly the DCCT (Diabetes Control and Complications Trial) for type 1 diabetes and the UKPDS (United Kingdom Prospective Diabetes Study) for type 2 diabetes.

The large volume of data from diverse populations has established strong justification for assigning an HbA1c cut point of ≥6.5% for the diagnosis of diabetes. 2 In 2010, the American Diabetes Association (ADA) considered the HbA1c (≥6.5%) as another criterion for the diagnosis of diabetes. 3

In spite of the widely accepted recent concept to use the HbA1c assay for both chronic management and diagnosis of diabetes, there are some conditions that may require a specific HbA1c method or may preclude its testing. These conditions include some hemoglobin traits, changes in red cell turnover, age factor, and racial disparities; however, it is premature to establish race-specific diagnostic values. 2

In 2008, only the ADVANCE trial (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation) demonstrated reduction in cardiovascular (CV) death by 12%, and 65% reduction in end-stage renal disease (ESRD). Neither ACCORD (Action to Control Cardiovascular Risk in Diabetes) nor the VADT (Veterans Affairs Diabetes Trial) demonstrated a statistically significant reduction in the primary combined CV end point. An unexpected 22% increase in total mortality was observed in the intensive arm (HbA1c<6%) of the ACCORD study, mainly due to increased CV mortality (CVM). In spite of more hypoglycemia in the intensive arm (threefold higher), the explanation behind this increasing CVM remains unclear. These trials suggested that patients with a shorter duration of disease and lower base HbA1c, without overt CV disease (CVD), benefitted more from intensive strategies. A meta-analysis of CV outcomes in these trials suggested that every HbA1c reduction of ≈1% may be associated with a 15% relative risk reduction in nonfatal myocardial infarction. 4

The accumulated results from the aforementioned type 2 diabetes CV trials suggest that the benefits of tight glycemic control varies, depending both on type of patients and the strategy by which this tight glycemic control is achieved. It follows that it is important to individualize targets and treatment strategies. 1 According to the latest ADA and European Association for the Study of Diabetes (EASD) position statement, more stringent HbA1c targets (6.0%-6.5%) might be considered in patients with short disease duration, long life expectancy, and no significant CVD. Conversely, a less stringent HbA1c goal (7.5%-8% or even slightly higher) may be more suitable for patients with a history of severe hyperglycemia, limited life expectancy, advanced complications, extensive comorbidities, or established vascular complications, and even for those in whom the target is difficult to achieve due to less motivation and nonadherence or limited resources and support systems. 5

Finally, the desires and values of the patient should be considered, since the achievement of any degree of glucose control requires active participation and commitment. 6

HbA1c targets: does one size fit all?

References
Glycated hemoglobin (HbA1c) is not a one-size-fits-all target in type 2 diabetic patients, and it should be adjusted to the clinical condition of the patient. The UKPDS (the United Kingdom Prospective Diabetes Study) showed that interventions for glycemic control targeting an HbA1c of 7% significantly decreased risk of microvascular complications.1 Furthermore, these benefits persisted over the longer term despite glycemic control similar to patients who were not treated to target.2 Subsequently, the ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation) study demonstrated that a greater reduction in HbA1c to a near normal level of 6.5% with a gliclazide MR– and metformin-based treatment regimen further reduced vascular risk to a significant degree.3 Achieving, as far as possible, near normal glycemic control is therefore central to the prevention of complications in type 2 diabetes. However, pursuing this with a non–gliclazide-based treatment strategy requires much greater effort, with substantially increased risk of hypoglycemia and mortality. This was observed in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial,4 which also attempted near normal glycemic control based on a treatment regimen of mostly glimepiride, metformin, glitazones, and insulin.

It is against this background that the mortality risk in attempting a uniform, one-size-fits-all HbA1c control target for all patients may outweigh the vascular benefits of glycemic control. While epidemiological studies support lowering of HbA1c from 7% to 6% because of a further reduction in microvascular risk, they also point to a curvilinear relationship between HbA1c and microvascular complications. Therefore, at the population level, the greatest number of complications will be averted by moving patients from very poor to fair or good, rather than “best possible” near normal glycemic control.5

Thus, for maximum risk benefit, the treatment target should be adjusted to the clinical condition of the patient. For individual patients with little comorbidity and long life expectancy, who stand to gain the most from a further lowering of HbA1c to below 7%, glycemic targets that are as close to normal as possible may be adopted, provided hypoglycemia is not a problem. On the other hand, less stringent HbA1c goals of around 7% are recommended for patients with one or more of the following characteristics: susceptibility to severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, and extensive comorbid conditions. A loosened HbA1c target would also be appropriate for those with long-standing diabetes in whom the general goal is difficult to attain despite effective doses of multiple glucose-lowering agents including insulin.6

References
In December 2011, a document entitled “The consensus of the Russian Association of Endocrinologists (RAE) on the initiation and intensification of glucose-lowering therapy in type 2 diabetes mellitus” was adopted in Russia. This document describes the decision made on individualization of glycated hemoglobin (HbA1c) targets for each patient with type 2 diabetes mellitus, depending on the patient’s age or life expectancy, disease duration, presence of vascular complications, and risk of hypoglycemia. It is also noted that other factors may influence individual HbA1c targets, such as motivation, compliance with therapy, patient education, and use of other treatments (Table). A decision was also made about individualization of the rate of achievement of target HbA1c values.

The consensus was based on the results of recently completed studies: ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation), and the VADT (Veterans Affairs Diabetes Trial). ACCORD showed that excessively rapid and aggressive adjustment of therapy is associated with increased risk of hypoglycemia and cardiovascular mortality. ADVANCE showed that a gradual and smooth achievement of glycemic targets helps avoid frequent hypoglycemic episodes, and thus reduces microvascular and macrovascular complications.

**Table.** Individual targets of HbA1c in type 2 diabetes mellitus.

<table>
<thead>
<tr>
<th>Age</th>
<th>No complications</th>
<th>No risk of hypoglycemia</th>
<th>Severe complications and/or risk of hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young</td>
<td>&lt;6.5%</td>
<td>&lt;7.0%</td>
<td>&lt;7.0%</td>
</tr>
<tr>
<td>Middle</td>
<td>&lt;7.0%</td>
<td>&lt;7.5%</td>
<td>&lt;7.5%</td>
</tr>
<tr>
<td>Elderly expectancy &lt; 5 years</td>
<td>&lt;7.5%</td>
<td>&lt;8.0%</td>
<td></td>
</tr>
</tbody>
</table>

**Commentaries on individualized HbA1c targets:**

- Patient age is not a clear-cut variable on which to base goals for glycemic control, as the age-related functional deterioration of organs and systems in each person is strictly individual. Therefore, in parallel with the relative concepts of “young”, “medium” and “old” age, there is a concept of “life expectancy” (LE), which better determines the estimated overall condition of the patient and likelihood of vascular complications. In patients of young and middle age with high LE, stricter goals for glycemic control are proposed in order to prevent the development of microvascular and macrovascular complications in type 2 diabetes mellitus. In patients with an LE of <5 years, the target for glycemic control may be less strict regardless of age, because LE in such patients is usually determined by other disorders (eg, cancer).

- The presence of severe diabetic complications (especially cardiovascular in nature) imposes certain restrictions on the setting of individual targets for glycemic control. The above mentioned studies, ACCORD and the VADT, have shown that in the presence of cardiovascular complications, treatment targeting normoglycemia is dangerous due to potential development of hypoglycemic states, which lead to cardiovascular and cerebrovascular events.

- The risk of severe hypoglycemia sharply limits the ability to achieve strict glycemic control, as it poses the risk of cardiovascular events. According to the VADT, prevalent severe hypoglycemia increases the risk of cardiovascular mortality almost fourfold and exceeds other risk factors by importance, such as age, presence of dyslipidemia, and cardiovascular disease.

The decision of the RAEs is fully congruent with the opinion of Ismail-Beigi and collaborators, who are also considering the possibility of a differentiated approach to the setting of targets for glycemic control according to a patient’s risk for hyperglycemia-related complications, comorbid conditions, psychological status, capacity for self-care, economic considerations, and family and social support systems.

**References**

For many years, we have treated diabetic patients to achieve target HbA1c values recommended by international guidelines and thus decrease the risk of microvascular and macrovascular complications. According to the American Diabetes Association (ADA), the goal for type 2 diabetic patients has been to lower HbA1c below 7%. However, for many people, tight control led to many episodes of hypoglycemia, which are potentially dangerous, especially in older patients, those with a history of heart disease, and those with diabetes for a long duration. Consequently, the goal to reach an HbA1c level below 7% did not necessarily prolong or improve quality of life in such people.

The importance of tight glycemic control in decreasing microvascular complications was well illustrated in the UKPDS (United Kingdom Prospective Diabetes Study), which showed that lowering HbA1c levels to 7% or less was related to a decrease in neuropathy, nephropathy, and retinopathy. For every 1% drop in HbA1c, a 33%–37% reduction in each of these microvascular complications occurred.

The relationship between blood glucose and macrovascular complications, however, appears to be more complex. The UKPDS 10-year follow-up showed the importance of lowering glucose immediately following diagnosis. In patients that were initially assigned to intensive treatment and who reached an HbA1c of 7%, compared with those assigned to conventional therapy and who reached an HbA1c of 7.9%, reduced rates of myocardial infarction and total mortality were maintained over 10 years, in spite of the fact that the difference in mean HbA1c between the two groups was lost after the first year of posttrial monitoring.

Based on these results, clinicians expected that reducing HbA1c would lower cardiovascular (CV) risk. However, concerns regarding the benefits of intensive glycemic control on macrovascular outcomes in type 2 diabetic patients, driven by the results from ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation), and the VADT (Veterans Affairs Diabetes Trial), have contributed to uncertainties in clinical practice decision making. None of these trials demonstrated that an intensive glycemic approach statistically significantly decreased CV end points.

These trials included patients that were older (by 8 to 10 years) than those in the UKPDS, and who had diabetes for a duration of 8 to 11.5 years. From 32% to 40% of the patients had a history of CV disease; in comparison, the UKPDS included newly diagnosed type 2 diabetes patients, of whom only 7.5% had a history of CV disease.

In ACCORD and the VADT, patients were randomized to intensive management using multiple combinations of oral agents, whereas the intensive approach in ADVANCE was based on gliclazide. ACCORD and the VADT aimed at an HbA1c of <6.0%, and ADVANCE at ≤6.5%. ACCORD patients on intensive treatment showed a 22% increase in total mortality, mainly driven by CV mortality. However, the rates of hypoglycemia and reduction in HbA1c level were not recognized as factors responsible for adverse outcomes. ADVANCE showed a 12% reduction in CV death and a 21% reduction in nephropathy, with a 30% reduction in the development of macroalbuminuria, a well-established marker of increased CV risk.

A meta-analysis of all these studies has proved that tight glycemic control significantly reduces coronary events without increasing the risk of death, emphasizing that in everyday clinical practice, the HbA1c goal should be tailored to each patient. While a tight HbA1c target of 6.0% to 6.4% can be considered in newly diagnosed type 2 diabetic patients, in older patients with longer disease duration and comorbidities requiring multiple medications, a higher target of 7.5% to 8.0% seems to be more appropriate.
Until recently, most diabetologists believed in the glucocentric approach to diabetes management. Common belief was that glycemic control was most important, and the lower the glycated hemoglobin (HbA1c), the fewer complications the patient would have. However, the classic UKPDS (United Kingdom Prospective Diabetes Study) has already raised some questions about this line of thinking, showing that patients with type 2 diabetes that received intensive treatment did not exhibit significant differences in cardiovascular events and mortality rates from those treated conventionally. Nevertheless, the lower rate of microvascular events observed in patients receiving intensive treatment supports the intensive strategy and lower HbA1c targets.

In addition to a continuous reduction in microvascular risk, the 10-year UKPDS follow-up has shown a reduction in the emerging risk of myocardial infarction and death from any cause in patients treated intensively, suggesting that the length of treatment is important in the evaluation of macrovascular complications and that lower glycemic targets are important from the very beginning. However, these patients from the UKPDS had recently been diagnosed with type 2 diabetes. On the other hand, the VADT (Veterans Affairs Diabetes Trial) showed that in patients with type 2 diabetes lasting 11.5 years and poor metabolic control, of whom 40% had had a previous cardiovascular event, the intensive treatment (HbA1c reaching 6.9%) vs conventional treatment (HbA1c of 8.4%) did not have a significant effect on major cardiovascular event rates, death, or microvascular complications, except for the progression of albuminuria.

The Steno-2 study perhaps had the greatest influence on the drop in popularity of the glucocentric approach in diabetes management, showing that intensive intervention with multiple drugs, aimed at several different cardiovascular risk factors, in addition to behavioral modifications had beneficial effects with regard to vascular complications, cardiovascular death rates, and death from any cause. In that same year, ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation) and ACCORD (Action to Control CardioVascular Risk in Diabetes) investigated whether the intensive glucose control strategy targeting strict glycemic goals (HbA1c ≤6.5% in ADVANCE and <6% in ACCORD) could reduce cardiovascular events in patients with type 2 diabetes for 8 to 10 years, respectively, and for which a large percentage already exhibited established macrovascular disease. In spite of a few differences in the results of the two studies, they showed that rigid glycemic control for this patient profile, over a period of 3.5 to 5 years, does not reduce cardiovascular events and can even be harmful.

Thus, the new American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) joint statement seems very sensible, targeting a treatment focused on the patient. I share the opinion that a patient’s health must be evaluated as a whole, considering all risk factors to their health, whether cardiovascular or not: for instance, a fall, caused by a hypoglycemic event, could be extremely deleterious to an elderly patient. That is why, on the one hand, faced with a relatively young patient who has just recently been diagnosed with type 2 diabetes and who has no other major risk factors, our treatment strategy must aim for normoglycemia. On the other hand, faced with an elderly patient with established vascular complications, we must be much more compliant about the glycemic level, aiming for targets that do not increase risk of hypoglycemia, considering the obvious health problems it could lead to. Of course, all other risk factors must be treated simultaneously, using the same criteria to evaluate the patient. I am thus firmly convinced that we must tailor HbA1c targets to individual patients.

HbA1c targets: does one size fit all?

References
Professional organizations recommend a glycated hemoglobin (HbA1c) target between 7% and 6.5% for diabetes control, while stressing the importance of early diagnosis, treatment individualization, and prevention of microvascular and macrovascular complications. Arguments for an individualized approach are based on data from clinical trials and epidemiological studies consistently showing early and intensive glycemic control reduces the risk of microvascular complications, but showing lack of a benefit for macrovascular outcomes. Ten-year follow-up data from the UKPDS (the United Kingdom Prospective Diabetes Study) reported a 24% decrease in risk of microvascular complications in the intensive sulfonylurea/insulin treatment group.1 These data were only partially supported by three major prospective randomized trials with the primary end point of major cardiovascular (CV) events conducted in elderly patients with long-standing type 2 diabetes and known cardiovascular disease (CVD). ADVANCE (Action in Diabetes and Vascular Disease: PreterAx and DiamicroN MR Controlled Evaluation) showed significant reduction in nephropathy (achieved HbA1c of 6.3%), and ACCORD (Action to Control Cardiovascular Risk in Diabetes) showed delay in the onset of albuminuria in intensive (achieved HbA1c of 6.3%) vs standard glycemic control; however, there was no benefit from the intensive strategy (achieved HbA1c of 6.9%) in the VADT (Veterans Affairs Diabetes Trial).2-4

The potential for intensive glycemic control to reduce CVD events in these studies is even more controversial. While ACCORD (HbA1c goal <6.0% vs 7.0%-7.9%) was stopped prematurely after a median duration of 3.5 years due to a 22% higher CV mortality with intensive therapy, especially in patients with a prior history of CVD or baseline HbA1c >8.0%, ADVANCE and the VADT saw no increase in overall or CV mortality in the intensive control arm (ADVANCE: HbA1c goal ≤6.5% vs that based on local guidelines; VADT: HbA1c goal <6.0% vs planned separation of 1.5%).5 Meta-analysis of these data showed that overall intensive therapy was associated with a significant 9% reduction in risk of major CV events, primarily because of a 15% reduction in risk of myocardial infarction (MI), and no effect on all-cause mortality during 4.4 years.6 Notably, in all these trials, allocation to more intensive control was associated with a significant increase in the risk of severe hypoglycemia, which occurred in <3% of intensively treated patients in ADVANCE, 16% in ACCORD, and 21% in the VADT.5 Subgroup analysis suggested that participants who had a shorter duration of diabetes, lower HbA1c, and absence of known CVD prior to randomization appeared to benefit from more-intensive glycemic control, whereas those with a history of macrovascular disease and long-term diabetes did not. Another important point to remember is that other CVD risk factors were corrected in all trials, using statins, blood pressure treatment, and aspirin therapy, which all are proven to reduce CVD risk. Thus, although on the population level the UKPDS 10-year results show significant reduction in MI (up to 33%) and in all-cause mortality (up to 27%)—supporting the hypothesis of an early glucose control benefit—individual factors should be considered for each patient when choosing the treatment goals and strategy.

In summary, there is evidence that good glycemic control with a target HbA1c <7.0% reduces risk of microvascular complications. For newly diagnosed and very motivated younger patients without known CVD and comorbidities, a lower target may be appropriate, while an HbA1c goal of >7.0% may be advised for elderly patients with advanced microvascular or macrovascular complications, long-standing diabetes, history of severe hypoglycemia, and short life expectancy. A holistic approach should be used, focusing on treating the patient as an individual and finding appropriate balance between the benefits and risks.

References
Diabetic is a major public health issue. In 2011, it was responsible for 8.2% of global mortality from any cause in people 20-79 years of age. In particular, it was responsible for 10% of vascular deaths (from coronary heart disease, stroke, and other vascular causes), 50% of end-stage kidney disease, and 11% of total health care expenditures in the world. Moreover, the prevalence of diabetes continues to grow rapidly and should reach 9.9% of the world population in 2030. Recent international guidelines from the American Diabetes Association/European Association for the Study of Diabetes and the International Diabetes Federation agree on an HbA1c goal of <7%. Unfortunately, not enough patients achieve optimal glucose control and maintain it over the long term. Thus, challenges in type 2 diabetes management consist of controlling blood glucose, maintaining this control over the long term, and preventing the development of microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular complications (myocardial infarction, peripheral arterial disease, and stroke). Beyond its secretagogue effect, which provides powerful control of blood glucose, Diamicron MR (gliclazide modified release) 60 mg has specific properties that make it a therapeutic option of choice in preventing decline in β-cell function and reducing the development of diabetic nephropathy or cardiovascular complications.

Diamicron (gliclazide) MR 60 mg: unique clinical benefits

Intensive glycemic control

Lowering blood glucose in order to reduce the risk of microvascular and macrovascular complications remains a major focus of type 2 diabetes therapy, as mentioned in the latest American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) guidelines. The various classes of non-insulin glucose-lowering drugs have different levels of efficacy in terms of glycated hemoglobin (HbA1c) reduction: high for metformin, sulfonylurea, thiazolidinedione, and glucagon-like peptide-1 (GLP-1); and intermediate for dipeptidyl peptidase-4 (DPP-4) inhibitor. The antidiabetic Diamicron MR (gliclazide modified release) 60 mg has proven its efficacy in monotherapy or in combination therapy in many clinical studies.

The GUIDE study (GlUcose control In type 2 diabetes: Diamicron MR versus glinEpidride) was carried out in 845 type 2 diabetic patients according to a double-blind, 27-week, parallel-group design. At the end of the follow-up, HbA1c had decreased...
by 1.3% in newly diagnosed patients treated with gliclazide MR in monotherapy.\(^2\) In the same study, the efficacy of gliclazide MR in combination with metformin was also analyzed. The addition of gliclazide MR to treatment regimens in patients uncontrolled by metformin led to a further significant 1.0% reduction in HbA\(_{1c}\) (HbA\(_{1c}\) lowered from 8.4% to 7.4%).

The ADVANCE study (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation) was conducted in 11,140 patients highly representative of those seen in daily clinical practice: mean age was 66 years old, mean duration of diabetes was 8 years, HbA\(_{1c}\)=7.5%, 32% had a history of macrovascular disease, and 10% had microvascular disease. At the end of the 5-year follow-up, the intensive strategy based on gliclazide MR had lowered HbA\(_{1c}\) by 1.0%, from 7.5% to 6.5%, and 80% of the patients had achieved an HbA\(_{1c}\) equal to or below 7%. Over 70% of the patients were taking the maximum dose of 120 mg of gliclazide MR.\(^3,4\)

A subanalysis of the ADVANCE study, aiming to examine the efficacy of the intensive gliclazide MR–based strategy showed that the efficacy of gliclazide MR was consistent across a wide variety of patient subgroups, defined by HbA\(_{1c}\), body mass index, duration of the disease, age, or previous treatment and treatment regimen at time of entry into the study. It is important to note that very large reductions in HbA\(_{1c}\) level (up to 4%) relative to baseline levels at entry were observed.\(^5\)

**Sustained glycemic control**

Sustained glycemic control remains a major issue in the management of type 2 diabetes. In the UKPDS (United Kingdom Prospective Study), the secondary failure rate of treatment was 44% after 6 years of diabetes.\(^5\) Riedel et al, in a retrospective study of 579 type 2 diabetic patients, found that 41.5% of patients who initially achieved target HbA\(_{1c}\), experienced secondary failure of treatment; the mean time to this occurrence was 1.3 years.\(^6\)

ADOPT (A Diabetes Outcome Progression Trial), conducted in 4,380 patients, showed a cumulative incidence of secondary failure of 21% with metformin, 34% with glyburide, and 15% with rosiglitazone at 5 years.\(^7\) Finally, in another retrospective analysis, the incidence of therapeutic failure (HbA\(_{1c}\)≥8%) in 2,220 patients was assessed in primary care practices in the United Kingdom.\(^8\) The results showed that 68% of patients who initially achieved an HbA\(_{1c}\) level of less than 7.0% had an HbA\(_{1c}\) level that exceeded 8.0% within 4 years.

Progressive decline in β-cell function, leading to a decline in insulin secretion, is recognized to play a major role in the deterioration of glycemic control over the long term in type 2 diabetes.\(^9\) Thus, antidiabetic treatments that protect β-cell function may represent a valid therapeutic option to reduce secondary failure of glycemic control.

In the ADVANCE study, the HbA\(_{1c}\) target of ≤6.5% was achieved with an intensive strategy based on gliclazide MR, and this effect was obtained progressively over 36 months and remained stable thereafter, delaying the use of insulin by up to 44 months after randomization.\(^2\) This has also been documented in previous studies comparing gliclazide MR with other sulfonylureas, including one with glibeclamide.\(^10\) This study investigated the time interval before the initiation of insulin therapy, and found a significantly longer interval before the initiation of insulin with gliclazide (mean 14.5 years) than with glibeclamide (mean 8 years), along with better blood glucose control, as shown by HbA\(_{1c}\) values (6.8% vs 7.4%, respectively; P<0.0001). The authors conclude that these benefits might be explained by the direct protective effect of gliclazide MR 60 mg on pancreatic β-cell function.

**Protection of β-cell mass and function**

A decrease in β-cell mass, mainly due to apoptosis, is crucial in the development and progression of type 2 diabetes. The effect of different oral antidiabetic agents on this process has been widely studied, and the results are heterogeneous according to the drug used. It has been shown that exposure of isolated rodent islets, cells from a β-cell line, or human islets in culture to tolbutamide, glibenclamide, and glimepiride increases β-cell apoptosis.\(^11\) \(^12\) By contrast, gliclazide has been shown to have the unique property to reduce β-cell apoptosis. In a study conducted with a human β-cell line (MIN6), exposure to various concentrations of gliclazide for 48 hours did not affect the number of apoptotic cells (Figure 1).\(^11\) Another study demonstrated that in human β cells exposed to an intermittent high glucose concentration, gliclazide enhanced expression of the β-cell differentiation factor PDX-1 (pancreatic and duodenal homeobox 1) and the cell proliferation marker Ki-67.

**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD</td>
<td>Action to Control CardiOvascular Risk in Diabetes</td>
</tr>
<tr>
<td>ADOPT</td>
<td>A Diabetes Outcome Progression Trial</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CONTROL</td>
<td>COllaborators oN TRials Of Lowering glucose</td>
</tr>
<tr>
<td>DPP-4</td>
<td>dipeptidyl peptidase 4</td>
</tr>
<tr>
<td>ESKD</td>
<td>end-stage kidney disease</td>
</tr>
<tr>
<td>HbA(_{1c})</td>
<td>glycated hemoglobin</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>IMT</td>
<td>intima-media thickness</td>
</tr>
<tr>
<td>LDL</td>
<td>low-density lipoprotein</td>
</tr>
<tr>
<td>MR</td>
<td>modified release</td>
</tr>
<tr>
<td>NO</td>
<td>nitric oxide</td>
</tr>
<tr>
<td>ROS</td>
<td>reactive oxygen species</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>
The secretagogue with clinical benefits beyond insulin secretion – Ruiz

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The authors suggest that beyond protection against β-cell apoptosis, gliclazide may also positively influence β-cell regeneration.13

Kidney protection

Renal disease is the most frequent complication for type 2 diabetic patients. Approximately 24.9% of patients develop microalbuminuria, 5%-20% develop macroalbuminuria, and 20%, a renal functional impairment (moderate to severe: estimated glomerular filtration rate <60 mL/min).14-16 In most Western populations, diabetes is the leading cause of end-stage kidney disease (ESKD),17 and about 20% of diabetic patients die from kidney disease.18

Diabetic nephropathy contributes to the burden of morbidity, increases the risk of premature death and affects the quality of life of the patients. In addition, renal impairment alters handling, and therefore effectiveness, of antidiabetic drugs by modifying pharmacokinetic and pharmacodynamic parameters. Thus, preventing kidney disease in patients is another major issue in the management of type 2 diabetes. The effectiveness of gliclazide MR 60 mg throughout the clinical course of kidney disease has been demonstrated, from the earliest stage (microalbuminuria) to the latest stage (ESKD). In the ADVANCE study, the strategy based on gliclazide MR reduced the risk of new-onset microalbuminuria by 9% (P=0.02), macroalbuminuria by 30% (P<0.001), new or worsening nephropathy by 17% (P=0.03), and ESKD by 12% (P=0.02) compared to placebo, with a favorable safety profile.19

Heterogeneity:

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Risk ratio, M-H, Random (95% CI)</th>
<th>Risk ratio, M-H, Random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD</td>
<td>0.91 (0.73-1.15)</td>
<td>0.91 (0.73-1.15)</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>0.35 (0.18-0.70)</td>
<td>0.35 (0.18-0.70)</td>
</tr>
<tr>
<td>UKPDS 33</td>
<td>0.74 (0.33-1.67)</td>
<td>0.74 (0.33-1.67)</td>
</tr>
<tr>
<td>UKPDS 34</td>
<td>1.20 (0.17-8.49)</td>
<td>1.20 (0.17-8.49)</td>
</tr>
<tr>
<td>VADT</td>
<td>0.64 (0.25-1.64)</td>
<td>0.64 (0.25-1.64)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>0.69 (0.46-1.05)</td>
<td>0.69 (0.46-1.05)</td>
</tr>
<tr>
<td>Total events</td>
<td>174</td>
<td>174</td>
</tr>
</tbody>
</table>

Test for overall effect: z=1.72; P=0.09

Figure 1. Effect of sulfonylureas and nateglinide on apoptosis in MIN6 cells.
The MIN6 cells were incubated with test media containing 1% fetal bovine serum and 5.5 mmol/L glucose with glibenclamide, gliclazide, glimepiride, and nateglinide at a concentration of 10 µmol/L. After 48 hours of incubation, apoptosis was evaluated by TUNEL assay (terminal deoxynucleotidyl transferase dUTP nick end labeling). A) Representative images of apoptotic cells. Arrows indicate brown-colored TUNEL-positive cells. B) Quantitative analysis of the rates of apoptotic cells induced by sulfonylureas and nateglinide. Data are expressed as mean percentage of control ± SEM (n=4). *P<0.01 vs control. #P<0.01 vs glibenclamide-treated MIN6 cells.


Figure 2. Pooled risk ratios, with 95% confidence interval, by trial for end-stage kidney disease (ESKD).

thy by 21% ($P=0.006$), and ESKD by 65% ($P=0.02$). Also, it is noteworthy that the intensive strategy based on gliclazide MR used in ADVANCE is the only one demonstrated to lead to significant reduction in ESKD. The UKPDS 33,21 UKPDS 34,22 ACCORD (Action to Control Cardiovascular Risk in Diabetes),23 and VADT (Veterans Affairs Diabetes Trial)24 all failed to demonstrate significant effects on ESKD (Figure 2, page 83).25 Moreover, gliclazide MR has been demonstrated to lead to regression of albuminuria by one stage in 62% of patients with albuminuria at baseline, with the majority achieving normoalbuminuria.26 All these results show that gliclazide MR 60 mg is effective in delaying or disrupting the long process of diabetic kidney disease in patients with type 2 diabetes. Even more interesting, gliclazide MR 60 mg is considered in the guidelines from the National Kidney Foundation Kidney Disease Outcomes Quality Initiative to be a preferred sulfonylurea in patients with chronic kidney disease, because it does not have active metabolites and does not increase the risk of hypoglycemia (Table I).26 The major route of elimination of gliclazide MR 60 mg and its metabolites is via the urine. Studies with radiolabeling indicate 60% to 70% urinary, and 10%

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Dosing recommendation CKD stages 3,4, or kidney transplant</th>
<th>Dosing recommendation Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-generation sulfonylureas</td>
<td>Acetohexamide</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
<tr>
<td></td>
<td>Chlorpropamide</td>
<td>Reduce dose by 50% when GFR &lt;70 and ≥50 mL/min/1.73 m²</td>
<td>Avoid</td>
</tr>
<tr>
<td></td>
<td>Tolazamide</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
<tr>
<td></td>
<td>Tolbutamide</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
<tr>
<td>Second-generation sulfonylureas</td>
<td>Glipizide</td>
<td>Preferred sulfonylurea No dose adjustment necessary</td>
<td>Preferred sulfonylurea No dose adjustment necessary</td>
</tr>
<tr>
<td></td>
<td>Gliclazide</td>
<td>Preferred sulfonylurea No dose adjustment necessary Not available in US</td>
<td>Preferred sulfonylurea No dose adjustment necessary Not available in US</td>
</tr>
<tr>
<td></td>
<td>Glyburide</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
<tr>
<td></td>
<td>Glimperide</td>
<td>Initiate at low dose, 1 mg daily</td>
<td>Avoid</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>Acarbose</td>
<td>Not recommended in patients with SCr &gt;2 mg/dL</td>
<td>Avoid</td>
</tr>
<tr>
<td></td>
<td>Miglitol</td>
<td>Not recommended in patients with SCr &gt;2 mg/dL</td>
<td>Avoid</td>
</tr>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td>Contraindicated with kidney dysfunction defined as SCr ≥1.5 mg/dL in men or ≥1.4 mg/dL in women</td>
<td>Avoid</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Repaglinide</td>
<td>No dose adjustment necessary</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td></td>
<td>Nateglinide</td>
<td>Initiate at low dose, 60 mg before each meal</td>
<td>Avoid</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Pioglitazone</td>
<td>No dose adjustment necessary</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td></td>
<td>Rosiglitazone</td>
<td>No dose adjustment necessary</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td>Incretin mimetic</td>
<td>Exenatide</td>
<td>No dose adjustment necessary</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td>Amylin analog</td>
<td>Pramlintide</td>
<td>No dose adjustment necessary for GFR 20-50 mL/min/1.73 m²</td>
<td>No data available</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>Sitagliptin</td>
<td>Reduce dose by 50% (50 mg/day) when GFR &lt;50 and ≥30 mL/min/1.73 m² and by 75% (25 mg/day) when GFR &lt;30 mL/min/1.73 m²</td>
<td>Reduce dose by 75% (25 mg/day)</td>
</tr>
</tbody>
</table>

Table I. Dosing adjustments by chronic kidney disease stage for drugs used to treat hyperglycemia. Adapted from the National Kidney Foundation.

Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation; CKD, chronic kidney disease; GFR, glomerular filtration rate; SCr, serum creatinine; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

to 20% fecal excretion. In the urine, hydroxymethyl and carboxymethyl, 6 α-, 7 α-, 6 β-, and 7 β-hydroxyl radicals, and 2 O-glucuronide conjugates are found, with only trace quantities of unchanged active ingredient.  

Cardiovascular protection

Type 2 diabetic people have risks for coronary heart disease, myocardial infarction, and stroke that are at least twofold higher than in nondiabetics.  

Cardiovascular death

<table>
<thead>
<tr>
<th>Trials</th>
<th>Number of events (annual event rate, %)</th>
<th>More intensive</th>
<th>Less intensive</th>
<th>∆HbA1c (%</th>
<th>Favors more intensive</th>
<th>Favors less intensive</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD</td>
<td>135 (0.79)</td>
<td>94 (0.56)</td>
<td>-1.01</td>
<td></td>
<td></td>
<td></td>
<td>1.35 (1.04-1.76)</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>253 (0.95)</td>
<td>289 (1.08)</td>
<td>-0.72</td>
<td></td>
<td></td>
<td></td>
<td>0.88 (0.74-1.04)</td>
</tr>
<tr>
<td>UKPDS</td>
<td>71 (0.53)</td>
<td>29 (0.52)</td>
<td>-0.66</td>
<td></td>
<td></td>
<td></td>
<td>1.02 (0.66-1.57)</td>
</tr>
<tr>
<td>VADT</td>
<td>38 (0.83)</td>
<td>29 (0.63)</td>
<td>-1.16</td>
<td></td>
<td></td>
<td></td>
<td>1.32 (0.81-2.14)</td>
</tr>
<tr>
<td>Overall</td>
<td>497</td>
<td>441</td>
<td>-0.88</td>
<td></td>
<td></td>
<td></td>
<td>1.10 (0.84-1.42)</td>
</tr>
</tbody>
</table>

In the ADVANCE trial, the intensive strategy based on gliclazide MR showed a clear trend in favor of a reduction in cardiovascular death by 12% ($P=0.12$). This result is even more relevant in light of the CONTROL meta-analysis, which reported a significant increase in cardiovascular mortality in the intensive arm of the ACCORD study (Figure 3).  

The positive trend observed in ADVANCE has been confirmed in recent data from two nationwide register studies including more than 70 000 patients with type 2 diabetes.  

The first study, published in the European Heart Journal in June 2011, was performed in more than 9000 Danish type 2 diabetic patients who had experienced a previous myocardial infarction, and included a 9-year follow-up. All patients included were treated in monotherapy at baseline. Of the different medications, gliclazide MR was the only sulfonylurea that was associated with a positive trend toward reduction in the risk of cardiovascular death compared with metformin, which was considered the reference treatment: 13% reduction ($P=0.40$) (Figure 4).
The second retrospective observational study was performed by Khandog et al in 64,188 patients also treated in monotherapy with glibenclamide, glipizide, or glimepride, and followed over 6 years. Compared with glibenclamide, glipizide was associated with lower risk of all-cause death (hazard ratio [HR] 0.33; 95% confidence interval [CI], 0.26-0.41) and cardiovascular mortality (HR 0.29; 95% CI, 0.21-0.38). The authors state that the better safety profile of glipizide MR 60 mg and certain specific and unique vascular properties may explain these differences.

The Steno-2 follow-up study (intensive treatment with glipizide as the sulfonylurea of choice versus conventional treatment), published in the New England Journal of Medicine in 2003, demonstrated a significant 53% reduction ($P=0.01$) in cardiovascular risk in the intensive-therapy group compared with the conventional-therapy group after 8 years. This difference is even more amplified at 13 years after a 5-year break from the study treatment. This cardiovascular benefit translates into a mortality rate that is cut by half.

These unique clinical benefits of glipizide MR 60 mg in terms of glycemic efficacy, β-cell preservation, and renal and cardiovascular protection may be explained in part, beyond its secretagogue effect, by its antioxidant properties. Indeed, chronic oxidative stress is postulated to be a key component in the pathogenesis of diabetes and the development of its complications.

Oxidative stress occurs when production of oxidants or reactive oxygen species (ROS) exceeds local antioxidant capacity. In the case of diabetes, hyperglycemia amplifies the glycolysis pathway in cells and thus increases ROS production by the mitochondrial chain.

This overproduction of ROS seems to play a key role in the decline of β-cell function and pathogenesis of vascular complications of diabetes, such as kidney dysfunction and cardiovascular disease.

**Oxidative stress and β-cell failure**

β Cells are extremely sensitive to oxidative stress. Indeed, β cells have a very low intrinsic antioxidant capacity, because they are low in free-radical quenching (antioxidant) enzymes such as catalase, glutathione peroxidase, and superoxide dismutase. In case of chronic exposure to hyperglycemia, ROS produced in excessive levels constantly “bombard” β cells, and this phenomenon is one of the main hypotheses to explain deterioration of β-cell function over time in type 2 diabetes.

Recent studies in type 2 diabetic animal models report that the progressive reduction in β cells is associated with excessive oxidative stress. Excessive apoptosis of β cells and defective insulin gene expression are both considered to be responsible for deterioration of insulin synthesis and secretion. This vicious circle contributes to the development and the progression of type 2 diabetes.

**Oxidative stress and kidney dysfunction**

It is postulated that localized tissue oxidative stress is a key component in the development of diabetic nephropathy. There remains controversy, however, as to whether this is an early link between hyperglycemia and renal disease or whether this develops as a consequence of other primary pathogenic mechanisms. In the kidney, a number of pathways that generate ROS such as glycosylation, specific defects in the polyol pathway, uncoupling of nitric oxide (NO) synthase, xanthine oxidase, NAD(P)H oxidase, and advanced glycation have been identified as potentially major contributors to the pathogenesis of diabetic kidney disease. In addition, a unifying hypothesis has been proposed whereby mitochondrial production of ROS in response to chronic hyperglycemia may be the key initiator for each of these pathogenic pathways. This postulate emphasizes the importance of mitochondrial dysfunction in the progression and development of diabetes complications including nephropathy.

**Oxidative stress and cardiovascular complications**

Oxidative stress induced by hyperglycemia increases cardiovascular complications by acting at several levels: increased vascular permeability, low-density lipoprotein (LDL) oxidation, prothrombotic activity, and through the inflammatory pathway. In particular, increased ROS production and reduced antioxidant defense promote LDL oxidation, which is an early step in the atherosclerotic process in diabetic patients. Additionally, oxidative stress and advanced glycation end product (AGE) deposition contribute to diabetic endothelial dysfunction, which has been described as the “choreographer” of diabetic vascular disease due to the microcirculatory changes it causes and its accelerating impact on macroangiopathic processes.

**Diamicron (glipizide) MR 60 mg: powerful antioxidant properties**

**Scavenger of ROS**

Glipizide is known to be a powerful general free radical scavenger. In cell-free assays, it has been shown to scavenge superoxide radicals, hydroxyl radicals, and NO in a dose-dependent manner, whereas glibenclamide was without effect. This unique scavenging effect of glipizide can be explained by its aminoazabicyclo-octyl ring, grafted onto the sulfonylurea group, which is thought to be a free radical scavenger.

These results were confirmed in a study using a cultured β-cell line (MIN6) to compare the effect of various sulfonylureas (glibenclamide, glimepride, and glipizide) or nateglinide on oxidative stress. Only glipizide was able to decrease production of intracellular ROS. All these findings show that glipizide MR 60 mg is not only effective in reducing blood glucose, but is also effective in reducing oxidative stress.

**Inhibition of LDL oxidation**

Oxidation of LDL in diabetic patients is promoted by increased free radical production from glucose oxidation and reduced...
Diamicron MR 60 mg: a remarkable safety profile

Diamicron (gliclazide) MR 60 mg: a remarkable safety profile

The risk of hypoglycemia and weight gain in the management of type 2 diabetes remains a main issue and the effect of antidiabetic treatment on these parameters is a key element in drug selection.

◆ Hypoglycemia

In the ADVANCE study, the intensive strategy based on gliclazide MR was associated with a very low risk of severe hypoglycemia: only 2.7% of the patients had at least one severe hypoglycemic episode. In ACCORD23 and the VADT,24 the rate of severe hypoglycemic events were 16.2% and 21.2%, respectively, in the intensive arm.

This observation has been confirmed recently in the Al Sifri study.56 The aim of this study was to assess the incidence of hypoglycemia with sulfonylureas (glibenclamide, glimepiride, and gliclazide) and the DPP-4 inhibitor (sitagliptin) in 1024 type 2 diabetic patients fasting during Ramadan. The proportion of patients who recorded one or more symptomatic hypoglycemic events was only 6.6% in the gliclazide MR group compared with 19.7%, 12.4%, and 6.7% in the glibenclamide, glimepiride, and sitagliptin groups, respectively.

◆ Weight

In the ADVANCE study, there was no weight gain in the group with intensive glucose control based on gliclazide MR, even in the obese patients.4 The authors conclude that a possible explanation is that the sulfonylurea used in the intensive glucose control arm was gliclazide MR.

In the UKPDS,21 ACCORD, and the VADT,24 the intensive strategy was associated with a weight gain of 1.7 kg, 3.5 kg, and 8.1 kg, respectively.

This unique safety profile of gliclazide MR 60 mg as regards hypoglycemia and weight compared with other sulfonylureas could be explained in part by its insulin secretion profile. Indeed, gliclazide MR restores the early peak of insulin secretion without inducing excess secretion of insulin during the second phase. The gliclazide MR–induced stimulatory effect on insulin release is reduced when the glucose level falls.56

Conclusion

Controlling blood glucose, maintaining this control over the long term, and preventing the development of microvascular and macrovascular complications are main challenges in type 2 diabetes management. Gliclazide MR 60 mg has an unmatched level of clinical evidence demonstrating powerful glycemic efficacy maintained over the long term, unique end-stage kidney disease prevention, cardiovascular safety, and an optimal safety profile in terms of hypoglycemia and weight gain. Moreover, it is postulated that oxidative stress, which is abnormally high in type 2 diabetic patients, has a negative impact on progression of diabetes by reducing β-cell function, and the development of diabetic nephropathy and cardiovascular disease, particularly by increasing atherosclerosis. Gliclazide MR 60 mg, thanks to its unique chemical structure, reduces oxidative stress, increasing the resistance of LDL to oxidation and slowing the progression of atherosclerosis in type 2 diabetic patients.
References


**Keywords:** antioxidant; β cell; cardiovascular protection; gliclazide; HbA1c; kidney protection; sustained glucose control

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**DIAMICRON LM (GLICLAZIDE): UN SÉCRÉTAGOGUE DONT LES BÉNÉFICIES CLINIQUES VONT AU-DELÀ DE LA SÉCRÉTION D’INSULINE**

Le diabète est un problème de santé publique majeur. En 2011, il était responsable de 8,2 % de la mortalité mondiale, toutes causes confondues, chez les personnes âgées de 20 à 79 ans. Le diabète est également responsable de 10 % des décès d’origine vasculaires (maladie coronaire, AVC et autres causes vasculaires), de 50 % des insuffisances rénales terminales et représente 11 % des dépenses totales de santé dans le monde liées au diabète. De plus, la prévalence du diabète continue à croître rapidement et devrait atteindre 9,9 % de la population mondiale en 2030. Les recommendations internationales de l’American Diabetes Association/European Association for the Study of Diabetes et de l’International Diabetes Federation publiées récemment accordent sur un objectif d’HbA1c <7 %. Malheureusement, trop peu de patients atteignent un contrôle glycémique optimal qui se maintient à long terme. Ainsi, l’obtention du contrôle glycémique, son maintien à long terme, la prévention du développement des complications microvasculaires (rétinopathie, néphropathie et neuropathie) et macrovasculaires (infarctus du myocarde, maladie artérielle périphérique et AVC) représentent les défis majeurs de la prise en charge du diabète de type 2. Au-delà de son effet sécrétagogue, qui permet un contrôle glycémique puissant, Diamicron LM (gliclazide à libération modifiée) 60 mg présente des propriétés spécifiques qui en font une option thérapeutique de choix dans la prévention de la dégradation de la fonction β-cellulaire et la réduction du risque de développer une néphropathie diabétique ou des complications cardiovasculaires.
How can today’s evidence-based proof in type 2 diabetes help us contain the diabetes epidemic?

Interview with M. Hirst, United Kingdom

Sir Michael Hirst was deputy chair of the International Steering Group for the campaign to secure a United Nations (UN) Resolution on Diabetes in 2006. From that vantage point, he reflects on what has subsequently been achieved in the wake of approval of the resolution by the General Assembly of the UN. The recent historic decision of the World Health Assembly to adopt the first ever global target to reduce by 25% preventable deaths from noncommunicable disease by 2025 is a welcome consequence of the global advocacy which has followed the UN resolution. He believes there is now unstoppable momentum for further action by member states to tackle the huge and growing economic, social, and human burden of diabetes and noncommunicable disease. He points to more focused advocacy in national and regional parliaments, urging national governments to invest in prevention strategies to slow the growth curve of new cases of type 2 diabetes—predicted in the absence of action to reach over 550 million by 2030. He has a clear view that clinicians, health care professionals, governments and health services, the pharmaceutical and food and drink industries, and people with diabetes all have a responsibility to work together to improve health outcomes and avoid the costly complications of diabetes. Sir Michael’s interest in diabetes started when his youngest child was diagnosed with type 1 while he was a member of the British Parliament. Successfully championing improved care for those with diabetes, he was invited to join the Board of Diabetes UK, eventually becoming its first nonmedical chair. In recognition of his work for diabetes, he was recently elected a fellow of the Royal College of Physicians of Edinburgh. Sir Michael became global president of the International Diabetes Federation in December 2012.

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It has been six years since the general assembly of the United Nations supported a resolution to make diabetes a global priority for action. What do you think have been the major advances since then?

The historic decision of the 65th World Health Assembly (WHA) in Geneva last month, whereby governments adopted the first ever global target to reduce preventable deaths from noncommunicable disease by 25% by 2025, is not only hugely welcomed by the international diabetes community, but can trace its roots to the United Nations (UN) Resolution 61/225 in December 2006 to make diabetes a global priority for action.
As deputy chair of the International Working Group for the UN resolution campaign, I well recall the initial opposition—primarily of the developed world—to the principle of a disease-specific resolution. With superb diplomatic skill, the Bangladeshi Mission at the UN led the campaign, persuading the Group of 77 (the 132 low- and middle-income countries) to support the resolution. The resolution recognized the significance of diabetes as an avoidable disease which is ruinously costly to national health systems and also undermines the achievement of the Millennium Development Goals. While it formally established World Diabetes Day as a UN-observed opportunity to raise awareness of diabetes, it also mandated member states to develop national policies for the prevention, treatment, and care of diabetes. This was, and remains, the first and only UN resolution on a noncommunicable disease.

The skeptics argued that the resolution would achieve little. Experience since then has, however, confounded them. UN-observed World Diabetes Day has proved a rallying point for raising awareness of diabetes all over the world. Hundreds of iconic buildings and structures are lit blue, the international color of diabetes, and in most countries the day is marked and used as a means of political engagement, people with diabetes being strongly to the fore in the awareness activity.

The resolution provided a convenient means by which national diabetes associations could hold their own governments to account for action on prevention, treatment, and care. There are countless examples of national governments timing their announcements on improvements to diabetes care to coincide with World Diabetes Day. The European Parliament provides a splendid example of what can be achieved for diabetes through imaginative campaigning. There, the four cochairs of the European Union Diabetes Working Group succeed in raising diabetes as an issue each month, and on 14 March 2012, the European Parliament approved the establishment of a strategic plan for diabetes in its 27 member states.

Quite apart from markedly greater national awareness activity, the resolution has spawned regional and European collaboration to support policy initiatives on diabetes. The European Coalition on Diabetes (a partnership of the EURopan Alliance for DIAbetes research[EURADIA], the Federation of European Nurses in Diabetes [FEND], Primary Care Diabetes Europe [PCDE], and the International Diabetes Federation [IDF] Europe) successfully promotes diabetes as an issue on a pan-European basis. FEND and IDF Europe have jointly produced their excellent and informative Policy Puzzle, a powerful tool for those engaged on advocacy for national plans and their implementation.

More broadly, the passing of Resolution 61/225 has provided a significant boost to international programs like Life for a Child, which does valiant work in poorer countries, providing insulin and essential medicines for children with insulin-dependent diabetes. Patient education—so vital in maintaining good glycemic control—has likewise benefited from educational initiatives like the IDF’s successful Diabetes Conversation Maps used in low- and middle-income countries.

It was always inevitable that the global campaigners for diabetes would not be content to stop at the UN resolution, and would be emboldened to think and act in an even more ambitious way. Influential figures like Sir George Alleyne in the Caribbean, an area where the high diabetes prevalence leads to thousands of limb amputations and premature deaths through end-stage renal failure, strokes, and heart attacks, pressed for further discussion and action at the global level to combat noncommunicable disease. The NCD Alliance (Non Communicable Disease Alliance)—a partnership of the IDF, the World Heart Federation, the Union for Cancer Control, and the International Union Against Tuberculosis and Lung Disease—came together in 2009 as a vehicle to campaign for action on noncommunicable disease. The UN resolution three years earlier had shown that the UN General Assembly could be persuaded of the importance of health, especially as a development issue, and skilful campaigning resulted in the UN High-Level Meeting on noncommunicable disease in September 2011 which approved a political statement on action to be taken by national governments in combating noncommunicable disease.

The decision at the WHA in May 2012 to adopt a target to reduce preventable deaths from noncommunicable disease by 25% is a further fruit of the process. The resolution, which the WHA adopted, aims to reach consensus on targets relating to the four main risk factors for noncommunicable disease: tobacco use, harmful use of alcohol, unhealthy diet, and physical inactivity. The IDF has played a notable part in the NCD Alliance in influencing governments to support a balanced set of targets that will tackle prevention via the risk factors, and treatment through availability of essential medicines.

The process of raising awareness of the destructive potential of diabetes as a precondition for global action, officially recognized in the UN resolution, is now an irreversible one. The strength of the arguments in support of global action is not disputed, but the solutions to the diabetes pandemic are neither easy nor inexpensive. The cost, however, of not acting is far greater. The IDF Diabetes Atlas, 5th edition, confirms that diabetes is neither easy nor inexpensive. The cost, however, of not acting is far greater. The IDF Diabetes Atlas, 5th edition, confirms...
that the prevalence of type 2 diabetes is rising in every country, every year, and the prevalence of impaired glucose tolerance (IGT) is likewise rising inexorably.

As the world now turns its attention to the post-2015 development framework as the successor to the Millennium Development Goals (which were expressly mentioned in the UN Resolution on Diabetes), it is of absolute importance that health is accorded the priority it merits in the new framework.

It is planned to convene a meeting of Parliamentary Champions for Diabetes at the next World Diabetes Congress in Melbourne in December 2013. Such an occasion will provide a further stimulus to global action on diabetes.

**Despite the conclusive evidence about the need for tight glycemic control, we can still see that the rate of glycemic control remains poor globally: what else can be done to further increase the type 2 diabetes control rate? And what are the responsibilities of the different health care players, from doctors to governments?**

No one can doubt that the rate of glycemic control is poor on a global basis. Given, however, the inadequacies of health budgets in so many of the low- and middle-income countries, it would be surprising if it were not so.

A number of initiatives and changes in practice could play an important part in improving glycemic control rates.

Earlier diagnosis is critical. Of the 35 million people in Europe with diabetes, it is estimated that 13 million are undiagnosed. Further, an estimated 42 million people have IGT, and, undetected and untreated, are already on the conveyor belt to a type 2 diagnosis. It is surely perverse that the remuneration systems in primary care provide no incentive for treatment to postpone the development and diagnosis of type 2 diabetes, but reward once formally diagnosed. Several important studies confirm the cost-effectiveness of early diagnosis and intervention. If more general screening cannot currently be afforded, there should be cardiovascular screening for the high-risk groups: the minority communities, women of childbearing years, people with a family history of diabetes, and those whose lifestyles evidently render them more susceptible to developing diabetes.

The recent European Diabetes Forum in Copenhagen, hosted by the Danish Presidency and Organization for Economic Cooperation and Development (OECD), heard from Prof Kamlesh Khunti who is leading the development of National Institute for Health and Clinical Excellence (NICE) guidance on screening for diabetes. He confirmed that screening for diabetes satisfies the World Health Organization (WHO) criteria for screening programs, highlighting effective self-assessment tests: Finn Risk developed by the Finnish Diabetes Association, and the online self-assessment developed by Diabetes UK which has already been used by over 133,000 people, with iPhone apps now being developed. Prof Khunti welcomed the UK’s National Health Service (NHS) Health Check, to which an HbA1c test is now being added.

Individualized care, with a personal care plan, would certainly make a positive difference, especially if sustained by proper patient education and reduced barriers to reimbursement, but no one should forget that we live in an age of austerity. As a nonclinician, I am not qualified to offer a view on polypharmacy, but who could contest that appropriate therapeutic intervention is essential to optimize health outcomes, and not just glycemic control.

The responsibility for improving the rates of glycemic control is broad. There should be a competent multidisciplinary team in primary and secondary care, appropriately skilled and with continuing professional education. The often overlooked comorbidity of depression in diabetes requires better access to specialist support. Government has a significant responsibility—right across government, rather than just the health “silos.”

There is a vital role for public health in the primary prevention of diabetes, through encouragement of physical exercise and healthier diets, as well as the practical means to do so—better urban design, like Rio de Janeiro; safe places to walk and cycle, like Copenhagen; the elimination of trans fats, championed by Mayor Bloomberg in New York; tobacco-free public places; the reduction of salt in line with current WHO recommendations where the UK is already leading the world. The person with diabetes also has a key responsibility to follow the advice of his/her health care team, and make whenever possible the necessary changes to lifestyle and diet.

All this assumes access to essential medicines and diagnostic support, yet we know that there are too many countries in the world where such access does not exist or cannot be guaranteed. Global advocacy is required here. There are the newer, more expensive medicines and therapies which can help to optimize control, but which may obviously be too costly for poorer countries. Impatient as we may be to see wholesale improvement, real progress will take years to achieve unless there is a seismic shift in the allocation of resources from communicable to noncommunicable disease, and determined action by national governments.

**The terms evidence-based and perception-based seem to explain the gap between international recommendations for the management of type 2 diabetes and current practice. Do you agree with this analysis? If yes, what can be done to move health care professionals towards evidence-based management of type 2 diabetes?**
Here are excellent recommendations for the management of type 2 diabetes. In reality, those of the American Diabetes Association (ADA), the Canadian Diabetes Association (CDA), the IDF, and the European Association for the Study of Diabetes (EASD) are broadly in line. Evidence-based recommendations do not, however, necessarily change practice, particularly where there are human and financial resource challenges.

Again, there is no single solution, no magic bullet. Sound professional education will help to close the gap, as will the monitoring of the individual practices in primary care, and the publication of outcomes. The lever of remuneration can help to reward achievement of targets in HbA₁c, blood pressure, lipid control, clinics for eye care and pregnancy, all of which matter in improving outcomes.

The role of private health insurance in many European countries is important in relation to evidence-based practice. The financial interests of private health insurers should surely encourage them to monitor evidence-based practice.

**Cost is a major factor in chronic disease management: can we today define a cost-effective management strategy for type 2 diabetes that at the same time satisfies the criteria of international recommendations?**

Cost is indeed a major factor in chronic disease management. While those who champion the interests of those with type 2 diabetes, like the IDF and its member associations, want the best possible care, that has to be qualified as the best affordable care. Many of the international recommendations assume a multidisciplinary care team which does not exist in many countries, while in others, the reality of care falls short of the desired standard. Too many health policy makers fail to appreciate that the costs of dealing with the complications of diabetes far outweigh the costs of trying to keep patients regularly checked, well controlled, and as healthy as possible.

There are, for example, excellent international guidelines on diabetic foot care developed by the International Working Group on the Diabetic Foot, and which have been translated into 26 different languages—surely a most welcome example of the spread of knowledge and best practice to improve care, particularly in low- and middle-income countries. The implementation of these guidelines would result in a cost-effective management strategy for good foot care, thereby reducing expensive amputations and the devastating effects upon the patient and his/her family, and the patient’s ability to earn a living and contribute to society. Yet, in too many countries, there is insufficient and inadequately trained staff, and a lack of the physical resources to provide the level of care recommended by the international guidelines. The pragmatic response has to be to encourage wherever possible the spread of knowledge and best practice, in the hope that training and training the trainers can help to bring up standards and prevent or mitigate avoidable complications.

We need to recognize the particular challenge in low- and middle-income countries. Unless chronic disease like diabetes is mainstreamed, there is a strong risk that it will be sidelined or ignored in favor of the infectious diseases which have had so much more attention by WHO and national governments.

**Following our conversation, it seems clear that we are in a continuous battle with type 2 diabetes. Do you think someday we will be able to win this battle?**

It has been depressing to note the constant growth in prevalence of type 2 diabetes as successive editions of the IDF Diabetes Atlas are published. At the time of the UN resolution campaign in 2006, 248 million people were estimated to have diabetes. Six years later, that number had risen by 50% to 371 million, with an even larger number estimated to have IGT. More shocking is the fact that half of those with diabetes remain undiagnosed and by definition untreated. Silently, but lethally, the disease attacks the macrovascular and microvascular systems with life-threatening consequences.

The principal challenge to global health policymakers is to break this cycle and constrain the growth of new cases by effective primary prevention. The causes of diabetes are well-known, as are the effective therapies, even if the resource is not always there to afford them. The actions which need to be taken have been identified, but compete with limited resources and the compelling nature of infectious diseases which can spook the political leaders. A wholesale shift in planning, resource, and action is needed if the growth curve is to reduce or even flatten. Finland stands out as an example of where concerted action for the past ten years under their Development Program for the Prevention and Care of Diabetes (DEHKO) has actually slowed the rate of new cases of type 2 diabetes.

I greatly admire the devoted work of clinicians and their health care professional colleagues in providing care and treatment for those with all forms of diabetes. Their success in helping people with diabetes to optimize their health outcomes, allied to the impressive range of medicines for diabetes, has enabled many patients to live longer and have more fulfilled lives than once would have been the case.

Advances in research, particularly into the epigenetics of type 2 diabetes, and more personalized medicine, identifying appropriate therapies for the genetics of the individual, should enhance both life expectancy and quality of life for the person with diabetes. But the battle against type 2 will never be won...
COMMENT LES PREUVES ACTUELLES SUR LE DIABÈTE DE TYPE 2 PEUVENT-ELLES NOUS AIDER À CONTENIR SON ÉPIDÉMIE ?

Sir Michael Hirst a été président adjoint de l’International Steering Group pour la campagne visant à obtenir une résolution des Nations Unies sur le diabète en 2006. Fort de cette expérience, il se penche ici sur ce qui a été réalisé dans la foulée de l’approbation de cette résolution par l’assemblée générale des Nations Unies. La décision historique récente de la World Health Assembly (Assemblée Mondiale de la Santé) d’adopter pour la toute première fois l’objectif de réduire de 25%, au niveau mondial, les décès évitables des maladies non transmissibles d’ici 2025 est une conséquence positive de l’action de sensibilisation mondiale qui a suivi la résolution onusienne. Pour Sir Michael, une dynamique a été créée qui mènera les états membres à entreprendre de nouvelles actions visant à s’attaquer aux conséquences humaines, sociales et économiques croissantes du diabète et des maladies non transmissibles. Il souligne la nécessité d’une prise de position plus ciblée des parlements régionaux et nationaux, qui pousserait les gouvernements nationaux à investir dans des stratégies de prévention permettant de ralentir l’augmentation des nouveaux cas de diabète de type 2, maladie qui devrait toucher 550 millions de personnes d’ici 2030 si rien n’est fait. Selon lui, les médecins, les professionnels de santé, les gouvernements, les services de santé, les industries alimentaires et pharmaceutiques et les diabétiques eux-mêmes doivent tous travailler de concert afin d’améliorer les effets néfastes du diabète sur la santé et en diminuer les complications coûteuses. L’intérêt de Sir Michael pour le diabète a débuté alors qu’il était membre du parlement britannique et qu’un diabète de type I fut diagnostiqué chez son plus jeune enfant. Suite au succès de sa campagne pour l’amélioration des soins délivrés aux diabétiques, il fut invité à siéger au conseil d’administration de l’association Diabetes UK dont il est par la suite devenu le premier président non médecin. En reconnaissance de son travail pour le diabète, il a été récemment élu membre du Royal College of Physicians d’Edinburgh. En décembre 2012, Sir Michael deviendra le président de la Fédération Internationale du Diabète.
In 2009, an International Expert Committee comprising representatives of the International Diabetes Federation (IDF), the American Diabetes Association (ADA), and the European Association for the Study of Diabetes (EASD) recommended measurement of glycated hemoglobin (HbA1c) as a diagnostic test option for diabetes (with a threshold of ≥6.5%) in addition to using glucose criteria. In 2010, the ADA adopted this criterion for the diagnosis of diabetes, and revised criteria for prediabetes diagnosis (impaired fasting glucose and impaired glucose tolerance), recommending that HbA1c values of 5.7% to 6.4% be used as an indicator of prediabetes. HbA1c testing offers some advantages, including lower day-to-day variability, less perturbation during periods of stress or illness, and requirement of a nonfasting sample. However, diagnosis based on HbA1c may identify individuals with type 2 diabetes or prediabetes that are distinct from those identified based on glucose criteria. The final goal would be to have a single universal diagnostic test for diabetes. Unfortunately, an increasing amount of evidence suggests that ethnic differences in HbA1c values may be present, and some clinical situations, such as anemia and hemoglobinopathies, interfere with accurate HbA1c measurement. Given the higher costs, which are unaffordable in many countries, the recommendation to use HbA1c as the only diagnostic test for diabetes on a global scale is not possible at present, and the glucose assay will continue to have an important role in the diagnosis of diabetes and prediabetes.

HbA1c ≥ 6.5%  
(The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay)  

or  
Fasting plasma glucose ≥ 26 mg/dL (7.0 mmol/L)  

or  
2-h plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an OGGT  

or  
Random plasma glucose ≥ 200 mg/dL (11.1 mmol/L)  
(In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis)

Table I. Criteria for the diagnosis of diabetes.  
Abbreviations: DCCT, Diabetes Control and Complications Trial; HbA1c, glycated hemoglobin; NGSP, National Glycohemoglobin Standardization Program; OGGT, oral glucose tolerance test.  

Factors contributing to variation in the glucose assay

Fasting plasma glucose  

FPG is the most commonly accepted diagnostic criterion for diabetes because the assay is available in most laboratories worldwide, inexpensive, easily automated, and requires a single sample. Nevertheless, fasting blood sampling interferes with daily activities, such as work, increasing the possibility that a person with type 2 diabetes will remain undiagnosed. Furthermore, FPG assessment has some limitations, including low reproducibility. For example, in a study from the Third National Health and Nutrition Examination Survey (NHANES III) that analyzed repeated assays from 685 fasting participants without diagnosed diabetes, only 70.4% of individuals with FPG ≥ 126 mg/dL on the first test were confirmed as having FPG ≥ 126 mg/dL when the analysis was repeated 2 weeks later. Several factors may contribute to this low reproducibility. FPG concentrations vary noticeably both in a single person from day to day (intraindividual variation in a healthy person is reported to be 5.7%-8.3%) and also between two or more people (interindividual variation in a healthy person is reported to be up to 12.5%). Thus, based on a coefficient of variation (CV) of 5.7%, FPG can range from 112-140 mg/dL in a person with an FPG of 126 mg/dL. Other factors may affect blood test results such as medications, venous stasis, posture, and sample handling. Plasma glucose concentration can be altered by prolonged fasting, physical activity, a hypocaloric diet for a week or more prior to testing, or food ingestion. Intercurrent illness, and acute stress can alter blood glucose concentrations. FPG has also a diurnal variation. A study of 12,882 participants in NHANES III who had no previously diagnosed diabetes revealed that mean FPG in the morning is considerably higher than in the afternoon.

Accuracy is another problem in basing diabetes diagnosis on the plasma glucose assay. Glucose concentrations decrease in the test tube by 5%-7% per hour as a consequence of glycolysis. To provide a correct assay of plasma glucose, the sample should be placed on ice water immediately and spun

Table II. Categories of increased risk for diabetes (prediabetes).  
Abbreviations: FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; OGGT, oral glucose tolerance test.  

Selected abbreviations and acronyms

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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>2-h PG</td>
<td>2-hour postload plasma glucose</td>
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<tr>
<td>ADA</td>
<td>American Diabetes Association</td>
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<tr>
<td>DCCT</td>
<td>Diabetes Control and Complications Trial</td>
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<td>FPG</td>
<td>fasting plasma glucose</td>
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<td>HbA1c</td>
<td>glycated hemoglobin</td>
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<td>IFG</td>
<td>impaired fasting glucose</td>
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<td>IGT</td>
<td>impaired glucose tolerance</td>
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<td>NGSP</td>
<td>National Glycohemoglobin Standardization Program</td>
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<td>National Health And Nutrition Examination Survey</td>
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<td>OGGT</td>
<td>oral glucose tolerance test</td>
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to isolate the plasma within 60 min. However, this is not the usual procedure followed in clinical practice. If the sample is left unprocessed at room temperature, the cells in the blood will continue to consume glucose, and consequently a sample with a true blood glucose concentration of 126 mg/dL would have a glucose concentration of about 110 mg/dL after 2 h. Rates of glycolysis are even higher in samples with increased concentrations of erythrocytes, white blood cells, or platelets.

The nature of the sample analyzed has a considerable influence on the glucose concentration assay. Glucose can be measured in whole blood, plasma, or serum, but plasma is recommended by both the ADA and World Health Organization (WHO) for diagnosis of diabetes.2,6 Nonetheless, numerous laboratories measure glucose in serum, and these values may differ from those obtained by measuring glucose in plasma. Glucose concentrations in whole blood are 11% lower than those in plasma because erythrocytes have a lower water content than plasma, depending also on hematocrit value.7 The majority of glucometers use whole blood for measuring glucose in capillary blood, but the results are not accurate in patients with anemia unless the meter measures hematocrit.8 In addition, capillary glucose concentrations can be 20%-25% higher than venous glucose during an OGTT,9 and thus is unpractical for the OGTT; however, capillary sampling is widely used, particularly in underresourced countries, and WHO considers capillary blood samples suitable for the diagnosis of diabetes.9

Glucose is measured in almost all laboratories using enzymatic methods, predominantly with glucose oxidase and with good precision (CV<2.5%). However, there is no program to standardize results among different automated instruments and different laboratories. In a study comparing serum glucose measurements performed in 6000 laboratories using 32 different instruments, a statistically significant difference in bias (deviation of the result from the true value) has been observed among laboratories, with biases ranging from –6 to +7 mg/dL at a glucose concentration of 100 mg/dL.11 These differences among laboratories can result in the potential misclassification of up to 12% of patients.2

**Oral glucose tolerance test**

One in three cases of undiagnosed type 2 diabetes in Europe will have nondiabetic fasting values, and therefore an OGTT will be required for diagnosis. The OGTT assesses the efficiency of the body to metabolize a standard dose of glucose (75 g) ingested orally. FPG and 2-h PG reflect different aspects of glucose metabolism. A combination of hepatic insulin resistance and defective early-phase insulin secretion resulting in excessive fasting hepatic glucose production contributes to fasting hyperglycemia. By contrast, a near-normal hepatic insulin sensitivity and marked muscle insulin resistance combined with defective late insulin secretion contribute to hyperglycemia after a glucose load.12 A rise in postprandial glucose concentration frequently occurs before fasting glucose increases. Therefore, postprandial glucose is a sensitive indicator of the risk for developing diabetes and an early marker of impaired glucose metabolism. In addition, compelling evidence suggests that elevated 2-h PG level during an OGTT is a better predictor of cardiovascular mortality or morbidity than FPG.13,14 However, the use of the OGTT for diagnosis of diabetes has several disadvantages. The OGTT is time-consuming and tiring for the person, expensive, and influenced by numerous medications and conditions other than diabetes; the dose of ingested glucose is unpalatable, and extensive subject preparation is required including ingestion of at least 150 g of dietary carbohydrate per day for 3 days prior to the test, a 10- to 16-h fast, and commencement of the test between 7:00 AM and 9:00 AM. In addition, the OGTT is subject to the same limitations as the FPG assay, as above described. Finally, a high degree of intrapersonal variability in the OGTT, with a CV of 16.7%, considerably greater than the variability for FPG, has been reported,15 resulting in poor reproducibility of the OGTT.15,16 For these reasons, the ADA recommends FPG measurement as the preferred glucose-based diagnostic test.3

**Factors contributing to variation in the HbA1c assay**

HbA1c is formed by glycation of the NH2-terminal valine residue of the β chain of globin. The average life span of erythrocytes is approximately 120 days and, therefore, HbA1c concentrations reflect the average glycemic exposure over the preceding 2-3 months. Chronic hyperglycemia is strongly associated with microvascular complications of diabetes. Observation studies show a strong correlation between HbA1c and such complications.17,18 In one study in which both FPG and HbA1c were measured, there was a stronger correlation between HbA1c and retinopathy than between FPG levels and retinopathy.19 Importantly, lowering HbA1c concentrations by tight glycemic control significantly reduces the rate of progression of microvascular complications, in particular retinopathy,20-24 and these findings have been used to establish the HbA1c treatment target for diabetes care.25 Taken together, these observations suggest that a reliable measure of glucose concentrations, such as HbA1c, which captures long-term glycemic exposure and is related to the risk of diabetes-specific complications, may serve as a better biochemical marker for the occurrence and severity of the disease than single or episodic measures of glucose levels.

HbA1c measurements offer some practical advantages over assessments of FPG or glucose levels during an OGTT. HbA1c levels have lower day-to-day variability, with a CV of <2%;26 they are not affected by recent food ingestion, intense exercise, stress, or illness, and samples can be taken at any time of the day and are stable for 1 week at 4°C; furthermore, concentrations predict the development of microvascular diabetes complications, and are used to monitor treatment. It is
Abnormal hemoglobin traits, such as HbS, HbC, HbF, HbD, and HbE affect some HbA\textsubscript{ic} measurements. The HbA\textsubscript{ic} assay is not appropriate in homozygous carriers of HbS or HbC, those with HbSC, or with any other variant that affects erythrocyte survival. Nonetheless, HbA\textsubscript{ic} can be measured accurately in heterozygous carriers of HbS, HbE, HbC, or HbD, and in individuals with increased HbF, provided an appropriate assay is used (an updated list is available at www.ngsp.org/ npsp.org/interf.asp). Despite these caveats, HbA\textsubscript{ic} can be measured accurately in the majority of people.

**Comparison of HbA\textsubscript{ic}, FPG, and 2-h PG criteria to diagnose diabetes and prediabetes**

Although it would be desirable for FPG, 2-h PG, and HbA\textsubscript{ic} values to be equivalent in identifying persons with diabetes or prediabetes, poor concordance between the three diagnostic criteria has been reported in different ethnic groups.\textsuperscript{36-40} We compared HbA\textsubscript{ic}, FPG, and 2-h PG criteria for the diagnosis of diabetes in adults from the US NHANES,\textsuperscript{36, 37} in a study in a cohort of older adults from the Rancho Bernardo Study,\textsuperscript{38} and in the Danish Inter99 study.\textsuperscript{39} In US adults from NHANES, moderate agreement existed for HbA\textsubscript{ic} and 2-h PG criteria for diagnosis of type 2 diabetes (κ coefficient = 0.427), with 81.8% of subjects classified as not having diabetes by both HbA\textsubscript{ic} and 2-h PG criteria, and 5.8% classified as having diabetes by both HbA\textsubscript{ic} and FPG criteria. Discordant classifications existed for 5.5% of individuals classified as not having diabetes by both HbA\textsubscript{ic} and FPG criteria, and 3.2% of subjects with HbA\textsubscript{ic} <6.5% and FPG <126 mg/dL and for 5.3% of subjects with HbA\textsubscript{ic} >6.5% and 2-h PG >200 mg/dL and for 6.9% of subjects with HbA\textsubscript{ic} <6.5% and 2-h PG >200 mg/dL. Finally, moderate agreement existed for HbA\textsubscript{ic} and FPG and/or 2-h PG criteria for diagnosis of type 2 diabetes (κ coefficient = 0.446), with 80.1% of subjects classified as not having diabetes by both HbA\textsubscript{ic} and FPG and/or 2-h PG criteria, and 7.0% classified as having diabetes by both HbA\textsubscript{ic} and FPG and/or 2-h PG criteria. Discordant classifications existed for 4.3% of subjects with HbA\textsubscript{ic} ≥6.5% and FPG <126 mg/dL and/or 2-h PG <200 mg/dL and for 8.7% of subjects with HbA\textsubscript{ic} <6.5% and FPG ≥126 mg/dL and/or 2-h PG ≥200 mg/dL (Figure 1).\textsuperscript{40} These results were in accord with those of two studies in adults from the US NHANES,\textsuperscript{36, 37} in a study in a cohort of older adults from the Rancho Bernardo Study,\textsuperscript{38} and in the Danish Inter99 study.\textsuperscript{39} In US adults from NHANES, moderate agreement was reported for HbA\textsubscript{ic} and FPG diagnoses (κ coefficient = 0.60), with 95.9% of the study participants classified as not having diabetes by both HbA\textsubscript{ic} and FPG and 1.8% classified as having diabetes by both HbA\textsubscript{ic} and FPG. Discordant classifications existed for 0.5% of individuals with HbA\textsubscript{ic} ≥6.5% and FPG <126 mg/dL and for 1.8% of subjects with HbA\textsubscript{ic} <6.5% and FPG ≥126 mg/dL.\textsuperscript{36}
In the Rancho Bernardo Study comprising 2107 adults without known type 2 diabetes, a low agreement existed for HbA1c and FPG and/or 2-h PG criteria for diagnosis of type 2 diabetes ($\kappa$ coefficient = 0.119), and 85% of participants with HbA1c $>6.5\%$ were classified as nondiabetic by FPG and/or 2-h PG criteria. The agreement for HbA1c and FPG criteria for diagnosis of type 2 diabetes was also low ($\kappa$ coefficient = 0.061). The same pattern was observed considering diagnosis of type 2 diabetes based only on the 2-h PG criterion ($\kappa$ coefficient = 0.112).

All together, these results suggest that individuals classified by HbA1c are different from those identified by the FPG or 2-h PG criteria. The discordance in the diagnosis of type 2 diabetes using diverse metabolic parameters is not completely unexpected because measurements of HbA1c, FPG, and 2-h PG may reflect different features of glucose metabolism. Fast ing hyperglycemia principally reflects hepatic insulin resistance and a dysfunction in the early phase of insulin secretion whereas postprandial hyperglycemia mainly reflects muscle insulin resistance and defects in late-phase insulin secretion. On the other hand, HbA1c may represent chronic exposure to both basal and postprandial hyperglycemia.

Since there is only a modest concordance between the FPG and 2-h PG tests to diagnose type 2 diabetes, there is not likely to be perfect concordance between HbA1c and either glucose-based test for diagnosis of categories at increased risk for diabetes (also referred to as prediabetes), which includes those with IFG and IGT. Considering the expected increased utilization of HbA1c as a screening criterion, it is important to evaluate the concordance among the three tests to identify subjects at increased risk for type 2 diabetes. To this aim, we examined the concordance of HbA1c, FPG, and 2-h PG tests for the identification of prediabetes in a cohort of white Italians comprising 780 nondiabetic individuals. Low agreement was found for HbA1c and FPG criteria for identification of subjects with prediabetes (IFG) ($\kappa$ coefficient = 0.332), with 56.3% of subjects determined to be without prediabetes according to both HbA1c and FPG criteria, and 15.8% classified as prediabetic by both HbA1c and FPG criteria. Discordant classifications occurred for 12.3% of subjects with HbA1c $<5.7\%$ and IFG, and for 15.6% of subjects with HbA1c values of 5.7%-6.4%, and FPG $<100\ mg/dL$. Low agreement existed for HbA1c and 2-h PG criteria for identification of subjects with prediabetes (IGT) ($\kappa$ coefficient = 0.299), with 53.3% of subjects determined to be without prediabetes according to both HbA1c and 2-h PG criteria, and 16.4% classified as having prediabetes by both HbA1c and 2-h PG criteria. Discordant classifications occurred for 15.3% of subjects with HbA1c $<5.7\%$ and IGT, and for 15.0% of subjects with HbA1c values of 5.7%-6.4%, and 2-h PG levels of $<140\ mg/dL$. Finally, a modest agreement existed for HbA1c and FPG and/or 2-h PG criteria for diagnosis of prediabetes, with 46% of individuals classified as not having prediabetes by both HbA1c and FPG and/or 2-h PG criteria, and 10.4% classified as having dia-

![Figure 1. Venn diagrams for diabetes.](image1)


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![Figure 2. Venn diagrams for prediabetes.](image2)

HbA1c levels reflect chronic glucose exposure, and are habitually utilized in monitoring glycemic control in order to guide therapy. HbA1c testing offers some practical advantages over assessments of FPG or 2-h PG, including lower day-to-day variability, less perturbation during periods of stress or illness, and requirement of a nonfasting sample. However, individuals identified as having type 2 diabetes or prediabetes according to HbA1c measurement may be distinct from those identified according to FPG and 2-h PG criteria; thus, if HbA1c screening is extensively implemented, it may to some extent change the present epidemiological setting of these dysglycemic conditions. The final goal would be to have a single universal diagnostic test for diabetes. Unfortunately, increasing evidence suggests that ethnic differences in HbA1c values may exist, and that some clinical situations, such as anaemia and hemoglobinopathies, interfere with accurate HbA1c measurement. Additionally, given the higher costs, which are unaffordable in many countries, recommendation to use HbA1c as the only diagnostic test for diabetes on a global scale is not feasible at present, and the glucose assay will continue to have an important role in the diagnosis of diabetes and prediabetes.

References

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HbA1c and postprandial glucose: diagnosis vs glycemic control monitoring – Sesti
L’HbA1c ET LE GLUCOSE POST-PRANDIAL : DOIVENT-ILS ÊTRE UTILISÉS COMME CRITÈRE DIAGNOSTIQUE OU SEULEMENT POUR CONTRÔLER LA GLYCÉMIE ?

En 2009, un comité d’experts internationaux comportant des représentants de l’International Diabetes Federation (la Fédération Internationale du Diabète), de l’American Diabetes Association (ADA ; l’Association Américaine du Diabète) et de l’European Association for the Study of Diabetes (EASD ; l’Association Européenne pour l’Etude du Diabète), a préconisé la mesure de l’hémoglobine glyquée (HbA1c) comme test diagnostique du diabète (avec un seuil ≥ 6,5 %) en plus de celle de la glycémie. En 2010, l’ADA a adopté ce critère pour le diagnostic du diabète, et révisé les critères de diagnostic du prédiabète (glycémie à jeun augmentée et tolérance au glucose diminuée), recommandant comme indicateurs de prédiabète des valeurs d’HbA1c de 5,7 % à 6,4 %. La mesure de l’HbA1c présente des avantages, tels qu’une plus faible variabilité d’un jour à l’autre, une moindre perturbation pendant les périodes de stress ou de maladie et le fait qu’elle ne nécessite pas un prélèvement à jeun. Cependant, le diagnostic basé sur l’HbA1c pourrait identifier des diabétiques de type 2 ou des prédiabétiques distincts de ceux dépistés par la mesure de la glycémie. L’objectif final serait d’avoir un seul test diagnostique universel pour le diabète. Malheureusement, il existe de plus en plus de preuves qui montrent que les valeurs d’HbA1c dépendent de l’ethnicité, et que certaines pathologies, telles l’anémie et les hémoglobinopathies, interfèrent avec sa mesure précise. Étant donné les coûts plus élevés, inabordables dans de nombreux pays, il est actuellement impossible de recommander l’HbA1c comme seul diagnostic du diabète à grande échelle, et la mesure de la glycémie continuera à jouer un rôle important pour détecter le diabète et le prédiabète.

Keywords: fasting plasma glucose; HbA1c; oral glucose tolerance test; prediabetes; type 2 diabetes
Until recently, cardiovascular disease (CVD) risk stratification in people with diabetes has been controversial. This review, based on evidence from the ADVANCE study (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation) and relevant publications identified via PubMed, examines existing approaches to CVD risk evaluation in diabetics, and discusses the use of absolute CVD risk tools as an appropriate basis for CVD prevention in such people. Evidence shows that diabetes is not a CVD risk equivalent in all circumstances. In diabetics, CVD risk follows a gradient. Reliably capturing this gradient depends upon assessing an adequate combination of risk factors. Many global CVD risk tools applicable to diabetics have been developed. Those derived from older cohorts are less accurate in contemporary populations and many newer tools have not been tested. The ADVANCE risk engine, recently developed from the large multinational ADVANCE study, performed acceptably in the ADVANCE population, and largely outperformed the popular Framingham risk equation when tested on the multinational DIABHYCAR (non-insulin–dependent DIABetes, HYpertension, microalbuminuria or proteinuria, CARdiovascular events, and ramipril) cohort of type 2 diabetics. In conclusion, the high-risk status conferred by diabetes does not preclude estimation of absolute CVD risk using tools such as the ADVANCE risk engine and its use in initiating and intensifying preventive measures. Adopting such an accurate and validated tool will likely improve therapeutic choices and outcomes in diabetes care.

Cardiovascular disease (CVD) risk estimation is motivated by the need to identify individuals whose outcomes can be modified by further investigation, initiation, or intensification of risk-modifying therapies. CVD risk estimates are also used to educate patients about their future chances of experiencing a cardiovascular event, encouraging adoption of healthy lifestyles and adherence to prescribed disease-modifying therapies in order to mitigate risk. Physicians engaged in routine care of individuals with diabetes are likely interested in quantifying patient risk of experiencing any major CVD outcome over a reasonable time horizon, using an accurate and validated global CVD risk evaluation tool.

Until very recently, strategies for CVD prevention in people with diabetes were guided by the principle that future chances of experiencing CVD in diabetics were similar in magnitude to those in nondiabetic individuals with existing CVD. Based on this
principle, diabetics were eligible for risk-reducing medications, such as statins, without accounting for absolute CVD risk levels. This principle, however, was inspired by evidence from earlier cohort studies,6,8 which may no longer reflect the modern era of diabetes care. Indeed, subsequent and more recent studies have shown variable results, with indications that the presence of diabetes mellitus may not be a “CVD risk equivalent” in all circumstances.9 These new findings have redirected interest on the need for a multifactorial approach to risk stratification for CVD prevention in diabetics. Such an approach is especially relevant in the current era, characterized by the gradual shift in diabetes mellitus management from a glucocentric focus to an intensive multifactorial strategy targeting reduction in the risk of both macrovascular and microvascular complications of diabetes.10,11

This review begins with a critical examination of the concept of diabetes mellitus as a CVD risk equivalent from various perspectives, and subsequently discusses the rationale and strategies for global CVD risk estimation in diabetics, emphasizing the specificities and limitations of such strategies. The discussion largely draws from new knowledge gained from cardiovascular disease risk modeling in the ADVANCE study (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation),3,12 and builds on the most up-to-date, relevant, and key literature regarding the concepts underlying use of prognostic models for global cardiovascular risk assessment in people with diabetes.

The concept of diabetes as a CVD risk equivalent

The concept of CVD risk equivalence was inspired by a study by Haffner et al.6 That study showed a nonsignificant difference in the risk of coronary heart disease (CHD) death in diabetics with no prior myocardial infarction (MI) compared with their nondiabetic counterparts with a history of MI. Accordingly, some guidelines have advocated widespread use of statins and aspirin in diabetic patients following the standards applicable to nondiabetic patients with a history of CVD.13-15 The study by Haffner et al.,6 however, was based on data collected between 1982 and 1990, well before the publication of landmark studies that have set the basis for contemporary diabetes care.16-20 Therefore, the study has many characteristics which may not reflect the profile of today’s diabetics. All study participants were white and were receiving glucose-control medications; thus, the study population likely included more individuals with an advanced stage of the disease. This differs from the typical contemporary community-based cohort comprised of diabetics with various degrees of disease severity.21 Other limitations of the Haffner study include likelihood of misclassification of CHD events during follow-up and low statistical power. Subsequent studies, based on larger cohorts, did not necessarily corroborate the findings of Haffner and collaborators. Two independent meta-analyses of available relevant studies do not support the concept of CHD equivalence.22,23 Furthermore, there is wide variation in the rate of CHD in diabetes, depending on the population and coincident CVD risk factors.22

Recent data on the potential harms of preventative therapies (statins or aspirin) do not encourage “blanket” use of such therapies irrespective of a patient’s absolute CVD risk. Indeed, two meta-analyses of relevant statin trials23,24 and a subsequent individual study25 have shown that statin use increases the risk of hyperglycemia. Therefore, statins may adversely affect the outcomes of glucose-lowering strategies if used too liberally, particularly in low-risk individuals who may not necessarily derive cardiovascular benefits. The potential nonbeneficial effect of the routine use of aspirin for primary prevention was illustrated in a recent meta-analysis, showing that in people without prior CVD (including those with diabetes), aspirin does not reduce cancer mortality as previously thought; it also did not reduce cardiovascular death, and it induced clinically important bleeding events.26 This underscores the importance of considering an individual’s absolute risk in clinical decision-making regarding aspirin in people with diabetes.

An overview of global risk assessment

Global cardiovascular risk assessment is based on the combination of predictive information from several risk factors, using mathematical equations (models).27,28 In those models, the coefficient of each included risk factor indicates its relative contribution to the overall CVD risk.27 Once developed, a risk model normally requires validation both on the derivation sample (internal validation) and on independent populations (external validation). Validation consists of testing whether the model correctly estimates the risk of future events in one or several populations.27

The performance of absolute cardiovascular risk models are commonly assessed in terms of discrimination, calibration, and, more recently, reclassification.27 Discrimination is the ability of the model to correctly classify individuals who go on to develop a cardiovascular event and those who remain event-free.27 For example, if there are two individuals with diabetes, with one developing a cardiovascular event after a
certain period of follow-up and the other remaining CVD free, a model with a high discriminative ability will systematically assign a higher risk to the first subject compared with the second. Discrimination is commonly characterized by the area under the receiver operating characteristic curve (AUC) or the C statistic. The C statistic ranges from 0.5 (lack of discrimination) to 1.0 (perfect discrimination). In general, a C statistic of 0.7 or greater is considered acceptable.

Calibration refers to the agreement between predicted risk and observed risk, and is assessed by comparing risk estimates from the model with actual event rates in the test population. For instance, a 5-year estimated risk of cardiovascular disease of 20% for a patient means that, in a given group of patients with similar characteristics, 20% will experience a cardiovascular event within a 5-year period of follow-up. The most commonly reported measure of calibration is the Hosmer-Lemeshow statistic. Estimates of calibration are sensitive to differing baseline levels of risk. For instance, if a given risk model is derived in a high-risk population, but tested in a low-risk population, the predicted risk estimates might be unreliably high. Recalibration of the risk model by adjusting the baseline risk estimates to fit the target population may help correct the overestimation or underestimation of risk.

Global CVD risk estimation in diabetes: contemporary approaches

Given that diabetes is not a CVD risk equivalent in all circumstances, treatment decisions in diabetes should be based not on reduction in relative risk, but on reduction of absolute risk. Therefore, in patients with diabetes, estimation of global absolute CVD risk is of utmost importance. Three main approaches have been used to estimate global cardiovascular risk in people with diabetes. The first approach, based on the CVD risk equivalent concept, consists of classifying all individuals with diabetes as having a 10-year absolute CVD risk of at least 20%. However, given the aforementioned evidence, such an approach appears to be counterintuitive as CVD risk is not uniformly distributed among people with diabetes. This is corroborated by many studies including a recent one showing multivariable risk in people with diabetes. Therefore, in patients with diabetes, estimation of global absolute CVD risk is of utmost importance. Three main approaches have been used to estimate global cardiovascular risk in people with diabetes.

The second approach consists of building unifying models for global CVD risk assessment for people with or without diabetes. The rationale for these tools is that there is no interaction between the diabetes status and other cardiovascular risk factors. In other words, everything else being equal, a subject with diabetes will not always have a higher risk than a nondiabetic subject with the same level of other risk factors (eg, blood pressure). This has been the basis for models such as the popular Framingham cardiovascular risk equations.

The third approach, termed the interaction approach, consists of constructing separate models for people with and without diabetes. This approach assumes that risk factors affect cardiovascular disease risk in different ways in people with and without diabetes. A main limitation of this approach resides in the fact that models developed in one group cannot be used to inform risk stratification in the other group. This approach in people with diabetes was initially used by the UKPDS (United Kingdom Prospective Diabetes Study) investigators. This was based on the assumption that a unit increment in the duration of diagnosed diabetes contributes more to risk estimates than a unit increment in age. Therefore, to allow a more rational use of predictive information from age in people with diabetes, it has to be split into two components (ie, age at diabetes diagnosis and known duration of diabetes). While the assumption has not necessarily been tested and confirmed in other studies, this consideration has other useful applications.

Available studies largely suggest that classical cardiovascular risk factors, including smoking, blood pressure, lipid variables, and even some novel risk factors affect the risk of CVD in similar ways in people with and without diabetes, with no evidence of interaction. Some risk factors or characteristics are likely to be more frequent in people with diabetes and may justify separate cardiovascular risk models for people with diabetes. These diabetes-specific characteristics include prescription of cardiovascular risk-reducing therapies, which may differ in people with and without diabetes. Additional specific factors, including glycated hemoglobin (HbA1c), urinary albumin excretion, and markers of microvascular complications of diabetes in general (especially retinopathy), have been demonstrated to be associated with CVD risk, and can contribute useful predictive information.

Performance of popular CVD risk models and the ADVANCE study

At the time the ADVANCE study was conducted, cardiovascular risk prediction models in the general population were dominated by models developed from the Framingham Heart Study, of which many were applicable to diabetics. Diabetes-specific models were also available, particularly those from the UKPDS study. However, the clinical utility and comparative performance of these models in contemporary populations with diabetes in diverse settings had not been established. Therefore, one major achievement was the implementation of extensive validation studies for popular existing cardiovascular risk models, using the unique features of the ADVANCE cohort. In the cohort of ADVANCE participants who had no known history of CVD at their enrolment in the trial, the 4-year risk of total cardiovascular events and particular components were largely overestimated by the Framingham-Anderson equations. Framingham-D’Agostino and UKPDS equations. This overestimation was also observed in males and females, whites and non-whites, and the double placebo cohort (ie,
those assigned to the placebo group in the blood pressure–lowering arm and the standard care group of the blood glucose–control arm.3 Discrimination of the Framingham and UKPDS equations in predicting CVD events in ADVANCE was poor for stroke, and modest-to-acceptable for CHD and total CVD. Recalibration substantially attenuated the magnitude of risk overestimation by the Framingham and UKPDS equations in ADVANCE. Discrimination, as expected, was unaffected, indicating the need for a new equation with improved discriminatory capability for people with diabetes, particularly those who are receiving many contemporary cardiovascular risk–reducing therapies.

Development of the ADVANCE model for cardiovascular prevention

In developing a new model for risk prediction, it is critical to account for the limitations of the existing ones in order to improve performance. In ADVANCE, the inclusion of participants from many countries provided the opportunity to take into account the substantial variation in the care of diabetes and CVD around the world, whereas other available models have been derived from homogeneous populations. The ADVANCE model targets total CVD and therefore captures the interaction between components of CVD, such as CHD or stroke, unlike many existing models that focus specifically on these components. The complexity of the relationship between chronic hyperglycemia and cardiovascular risk is less fully addressed in existing models. Some improvement was achieved in the ADVANCE model through integration of risk factors to capture the exposure to chronic hyperglycemia both prior to and after the clinical diagnosis of diabetes. Statistical method is an important component of model development. Trusted statistical methods have been used to select potential risk factors and test their suitability for inclusion in the ADVANCE risk engine.12

Table I. Standardized (β) coefficients (95% confidence intervals) and standard errors for predictors in the ADVANCE cardiovascular disease prediction model.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter estimate (standard error)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (per 1-y increase)</td>
<td>0.062 (0.008)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (female vs male)</td>
<td>-0.474 (0.098)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Known duration of diabetes (per 1-y increase)</td>
<td>0.083 (0.010)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse pressure (per 1-mm-Hg increase)</td>
<td>0.007 (0.003)</td>
<td>0.016</td>
</tr>
<tr>
<td>Retinopathy (yes vs no)</td>
<td>0.383 (0.101)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation (present vs absent)</td>
<td>0.601 (0.154)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (per 1% increase)</td>
<td>0.099 (0.027)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Log of urinary albumin/creatinine ratio (per 1-log-mg/g increase)</td>
<td>0.193 (0.033)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-HDL cholesterol (per 1-mmol/L increase)</td>
<td>0.126 (0.034)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treated hypertension (yes vs no)</td>
<td>0.242 (0.106)</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Table I. Standardized (β) coefficients (95% confidence intervals) and standard errors for predictors in the ADVANCE cardiovascular disease prediction model.


Risk factors considered for inclusion in the ADVANCE model were age at clinical diagnosis of diabetes, duration of diagnosed diabetes, sex, blood pressure indices (systolic, diastolic, mean arterial, and pulse pressures), lipid variables (total, high-density lipoprotein [HDL], and non-HDL cholesterol; ratio of total/HDL cholesterol, and triglycerides), body mass index, waist circumference, waist-to-hip ratio, blood pressure–lowering medication (ie, treated hypertension), statin use, current smoking, retinopathy, atrial fibrillation (past or present), urinary albumin/creatinine ratio, serum creatinine, HbA1c, fasting glucose, and randomized treatments (blood pressure–lowering and glucose-control regimens). Ten of these candidate risk factors were included in the final ADVANCE model. To improve the applicability of the ADVANCE equation to other populations, age at diabetes diagnosis and known duration of diabetes were preferred to age at baseline. The β coefficients and accompanying standard error for risk factors in the ADVANCE cardiovascular risk model are shown in Table I.12
Performance of the ADVANCE risk model
The applicability of the ADVANCE model was tested on the same population used to develop the model (ie, internal validation) and on an independent external sample for which the DIABHYCAR (non-insulin–dependent DIABetes, Hypertension, microalbuminuria or proteinuria, CAfiovascular events, and ramipril participants) cohort was used (ie, external validation). In both internal and external validations, the discrimination of the ADVANCE model was acceptable. In comparison with existing total CVD models, the ADVANCE model largely did better at ranking the DIABHYCAR (event vs no event) than the Framingham-Anderson and Framingham-D’Agostino models. The calibration of the ADVANCE model was excellent in internal validation and good in external validation, with only a modest risk underestimation, likely explained by the difference in the levels of preventive therapies between ADVANCE and DIABHYCAR populations. Interestingly, the agreement between predictions by the ADVANCE models and the observed CVD events was consistent across different cut-offs for predicted risk of CVD. For comparison,

Figure 1. Major cardiovascular disease points and 4-year predicted risk by the ADVANCE model equation.
As an illustration of the use of the risk scoring chart, a male subject, diagnosed with diabetes at the age of 50, who has a pulse pressure of 50 mm Hg and is currently treated for hypertension, and who since 3 years ago also has retinopathy, atrial fibrillation, and microalbuminuria, an HbA1c of 7%, and a non–HDL-C of 3.3 mmol/L will receive a total score of 13 points: 0 for sex, 3 for age at diagnosis, 1 for known duration, 1 for pulse pressure, 1 for treated hypertension, 1 for retinopathy, 2 for atrial fibrillation, 2 for microalbuminuria, and 1 each for HbA1c and non–HDL-C. A score of 13 points is equivalent to a 4-year estimated risk of 6.2%, which is similar to the risk estimated for the same patient using the full equation.

Abbreviations: ADVANCE, Action in Diabetes and Vascular disease: PreterAx and DemicroN MR Controlled Evaluation; CVD, cardiovascular disease; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol.
the two Framingham equations overestimated the risk of CVD in the DIABHYCAR cohort by 65% (Anderson equation) and 99% (D’Agostino equation). Using a cut-off for 4-year predicted risk of >8%, which is approximately equivalent to a 10-year predicted risk of 20% and above, the ADVANCE model would reliably identify the 22% of the ADVANCE participants and 39% of the DIABHYCAR participants in whom 48% and 66% of CVD events, respectively, occurred during follow-up. Further intensifying treatment in such groups on top of any baseline therapy could achieve significant gain in terms of cardiovascular risk reduction.

Dissemination of the ADVANCE model
To facilitate the uptake of the ADVANCE model in clinical practice, a handheld calculator and a risk scoring chart (Figure 1) have been developed. Other tools from this model, including an online calculator, are available on the model’s Web site, making it easily accessible and encouraging its adoption. These tools have undergone extensive validation to ensure they provide estimates similar to those from the full ADVANCE risk equation (Figure 2).

Performance of existing global risk tools for cardiovascular risk estimation in people with diabetes
Two systematic reviews have examined the performance of CVD risk estimation models applicable to people with diabetes. The most recent and comprehensive review described 45 risk models. Of these, 12 were specifically developed for patients with type 2 diabetes (including the ADVANCE model), and 33 were developed in the general population and used diabetes status as a predictor. These models vary greatly in quality and methodology used to develop them. A number of the prediction models were developed before the advent of novel and more appropriate statistical methods for assessing model performance. Only about one-third of the existing CVD risk tools applicable to diabetics have been externally validated in a population with diabetes.

The discriminative ability both for diabetes-specific CVD prediction models and general population prediction models using diabetes status as a predictor was generally acceptable-to-good (ie, C statistic ≥0.70). However, performance-assessment methods used in the validation studies and the discriminative ability in these models varied widely (C statistics: 0.61 to 0.86). The discrimination of prediction models designed for the general population was moderate (C statistics: 0.59 to 0.80) and calibration was generally poor.

The most commonly validated models were the general population–based Framingham cardiovascular risk equations and the diabetes-specific UKPDS risk engines. The Framingham prediction models also showed low-to-acceptable discrimination and poor calibration. Although the discriminative power of UKPDS engines was acceptable, calibration was poor and there was a tendency toward systematic overestimation of risk, particularly in recent cohorts. The models with best external validity were more contemporary, but were validated in other patient populations only once. Therefore, more validation studies on the performance of these prediction models in different diabetes populations are needed.

Conclusion
The quest for the best approaches to assess cardiovascular risk and thus prevent vascular complications in individuals with diabetes is a continuing pursuit. It is increasingly clear that diabetes is not a cardiovascular risk equivalent in all circumstances. The CVD risk is not uniformly distributed in individuals with diabetes, but rather follows a gradient. Adequately capturing this gradient depends on the combination of individual risk factors. Global risk assessment appears to be the way forward for managing CVD risk in people with diabetes. Both ADVANCE and subsequent studies have provided evidence that existing popular models derived from older cohorts are less accurate with regard to cardiovascular risk evaluation in a contemporary population with diabetes.
recognition of this nonoptimal performance and other limitations of existing models has stimulated efforts to develop new cardiovascular risk models (including the ADVANCE model) with improved predictive accuracy for people with diabetes. The ADVANCE model is unique in that it was developed from a contemporary multinational cohort of people with diabetes, and successfully validated in another recent multinational cohort of individuals with diabetes. Inclusion of participants from developing countries in the ADVANCE cohort contributes to the potential of the ADVANCE risk model in assisting cardiovascular risk stratification efforts in many settings around the world.

References


Keywords: ADVANCE risk model; ADVANCE study; cardiovascular; diabetes mellitus; performance; risk prediction

Le calculateur de risque ADVANCE pour prédire la maladie cardiovasculaire dans le contexte des stratégies actuelles d’évaluation du risque cardiovasculaire chez les diabétiques

La stratification du risque de maladies cardiovasculaires (MCV) chez les diabétiques était jusqu’à maintenant controversée. Cet article se base sur les résultats de l’étude ADVANCE (Action in Diabetes and Vascular disease : Preterax and DiamicroN MR Controlled Evaluation) ainsi que sur des publications pertinentes de PubMed, pour examiner, d’une part, les approches utilisées dans l’évaluation du risque de MCV chez les diabétiques, et d’autre part, l’emploi d’outils de risque absolu dans la prévention des MCV. Il a été démontré que le diabète n’entraîne pas le même risque de MCV dans tous les cas. Le risque de MCV suit un gradient chez les diabétiques. Pour appréhender ce gradient de façon fiable il faut évaluer une association ad hoc de facteurs de risque. De nombreux outils évaluant le risque global de MCV chez les diabétiques ont été développés. Ceux issus des anciennes cohortes ne sont pas adaptés aux populations actuelles et de nombreux outils plus récents n’ont pas encore été testés. Le calculateur de risque ADVANCE, développé récemment d’après l’étude multinational à grande échelle ADVANCE, a bien fonctionné dans cette population, et a donné de bien meilleurs résultats que l’équation de Framingham, pourtant très prisée, lorsqu’il a été appliqué à la cohorte multinationale de diabétiques de type 2, DIABHYCAR (non-insulin-dependent DIAbetes, Hypertension, microalbuminuria or proteinuria, CARdiovascular events, and ramipril). En conclusion, le risque absolu élevé de MCV lié au diabète n’empêche pas son estimation à l’aide d’outils comme le calculateur de risque ADVANCE et son utilisation dans la mise en place et l’intensification de mesures préventives. Adopter cet outil, validé et précis, améliorerait probablement les choix thérapeutiques et les résultats du traitement du diabète.
Napoleon's short-lived military campaign in Egypt (1798-1801) was all but a failure; yet from a cultural and scientific point of view, it was to have momentous consequences. It culminated in the publication by France's crème de la crème savants of the 23 mammoth volumes of the *Description of Egypt*—a comprehensive inventory of ancient and modern Egypt as well as of its natural history—and led to a veritable Egyptomania that engulfed Europe. Get ready for an exciting read with Roy and Lesley Adkins and Dr Christian Régnier as they tell us about the decipherment of hieroglyphs and the legacy of French medicine in Egypt.

The keys of Egypt: Jean-François Champollion

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French doctors in Egypt with Napoleon

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Rodriguously talented, Champollion became obsessed with ancient languages, initially in order to read the original Old Testament texts... He also became increasingly absorbed by ancient Egypt and started to learn Coptic and later Arabic with Dom Raphaël de Monachis, a Greek Catholic priest from Egypt, who taught at the Special School of Oriental Languages in Paris. Champollion was convinced that Coptic was the key to the Egyptian language and to deciphering hieroglyphs.

Jean-François Champollion was born on 23 December 1790 in the town of Figeac. He was sent to Grenoble in 1801 to live with his brother Jacques-Joseph and became obsessed by ancient languages and Egypt. At the age of sixteen he went to Paris to study for two years, and on returning to Grenoble he taught at its new university. He also continued researching hieroglyphs, but was frustrated with his copies of the Rosetta Stone, which had been discovered in Egypt during Napoleon’s expedition, though later handed over to the British. Champollion inadvertently contacted his rival Thomas Young in London, who was also trying to decipher hieroglyphs, finally unlocking the key to their decipherment. Their other books on ancient history include Empires of the Plain (2003) on the decipherment of cuneiform, Handbook to Life in Ancient Rome (1994), and Handbook to Life in Ancient Greece (1997). Their naval books are Trafalgar, published in 2004 for the battle’s 200th anniversary in 2005, The War for All the Oceans (2006), and Jack Tar (2008). Their latest book, Eavesdropping on Jane Austen’s England, will be published in 2013. They are Fellows of the Society of Antiquaries of London (FSA) and Members of the Institute for Archaeologists (MiFA). They live near Exeter in Devon. www.adkinshistory.com
The house at 28 rue Mazarine in Paris, where Jean-François Champollion lived and carried on his research into Egyptian hieroglyphs, was less than 200 meters from the Institute of France where his older brother Jacques-Joseph Champollion-Figeac worked at the Academy of Inscriptions and Literature. Towards midday on 14 September 1822, clutching his papers, Champollion fled along the narrow street, around the corner and into the Institute. Not fully recovered from his latest spell of ill-health, he was already breathless as he burst into his brother’s office, flung his papers on the desk and managed to shout “Je tiens l’affaire!” (I’ve got it!).

Champollion had been scrutinizing some highly accurate drawings of hieroglyphic inscriptions that the architect Jean-Nicolas Huyot had recently copied at the temple of Abu Simbel in Upper Egypt. After years of work, often interrupted by the ever-changing political situation, Champollion had at last spotted the system underlying the seemingly unintelligible hieroglyphs. He began to explain to Jacques-Joseph what he had discovered, but only managed a few words before collapsing unconscious on the floor. For a few moments his brother feared he was dead.

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Conquest of Egypt

Over one and a half thousand years had passed since anyone could read and write hieroglyphs, the ancient Egyptian writing system, because under Roman rule in Egypt the use of hieroglyphs declined with the rise of Christianity and the closure of pagan temples. The conquest of Egypt by the Arabs in 642 and the Ottoman Turks in 1516 meant that the country was closed to most western Europeans for hundreds of years. Even so, interest in hieroglyphs was rekindled in the early fifteenth century by the rediscovery of ancient Greek and Latin documents.

The story of decipherment really began with the invasion of Egypt by Napoleon in July 1798. Along with his military force of some 38 000 troops, there were also more than 150 civilian savants, including astronomers, engineers, linguists, poets, artists, musicians, and mathematicians. Less than a month later, on 1 August, disaster struck when the French fleet was destroyed by a Royal Navy fleet under Rear-Admiral Nelson in Aboukir Bay. In England, this battle became known, erroneously, as the “Battle of the Nile.”

Despite this military setback, the savants embarked on an extraordinary study of ancient and modern Egypt. Exploring as far south as Aswan in Upper Egypt, they were astonished at the ancient ruins, all covered in hieroglyphs. However, the chance discovery of a substantial stone slab caused particular excitement. It was unearthed during work on the defenses of the Fort St Julien near Rosetta in 1799 and had three inscriptions written in three different scripts (Greek, demotic and hieroglyphs) and yet only two languages (Greek and Egyptian). Although damaged, especially the hieroglyphic part, the Rosetta Stone appeared to offer a key for the decipherment of hieroglyphs. It did not take long for the Greek inscription (in uppercase letters) to be translated, revealing that it was a decree of the priests of Memphis, dated 27 March 196 BC, commemorating the pharaoh Ptolemy V Epiphanes. Although the savants managed to make copies of the three inscriptions, in 1801 the Rosetta Stone itself was handed over to the British as part of the spoils of war when the French capitulated.

Champollion’s beginnings

The reports and popular books written by the savants triggered a wave of Egyptomania across Europe, but the quest to decipher hieroglyphs had barely begun and was to cause years of rivalry, particularly between two scholars, the Frenchman Jean-François Champollion and the Englishman Thomas Young. Champollion was born on 23 December 1790 in the town of Figeac, in the Quercy region of France, and so was nearly eight years of age when Napoleon invaded Egypt. In March 1801, he left Figeac and traveled to Grenoble, over 300 kilometers away, to live with his brother Jacques-Joseph and where he received a more rigorous education. Prodigiously talented, Champollion became obsessed with ancient languages, initially in order to read the original Old Testament.
texts, because the Bible was believed to be the most reliable evidence for how the world began. He also became increasingly absorbed by ancient Egypt and started to learn Coptic with Dom Raphaël de Monachis when visiting Grenoble. A Greek Catholic priest from Egypt, Monachis taught Arabic at the Special School of Oriental Languages in Paris. Champollion was convinced that Coptic was the key to the Egyptian language and to deciphering hieroglyphs. At this stage, he thought that hieroglyphs comprised a simple alphabet and that he would eventually be able to match Coptic words with hieroglyphic ones. Although he was wrong, knowledge of Coptic would prove invaluable in working out ancient Egyptian words, and he was right to think that spoken Coptic had evolved from ancient Egyptian.

At the age of sixteen, in September 1807, Champollion went to Paris, where he studied for two years, dividing his time between the College of France, the Special School of Oriental Languages, the National Library, and the Commission of Egypt that was responsible for publishing the volumes of the Description de l’Égypte—the results of the work of Napoleon’s savants in Egypt. Intellectual and cultural Paris was without parallel in Europe, though Champollion disliked the city itself, where he suffered poverty, poor health, and threats of conscription into Napoleon’s army. On top of learning languages such...
The discovery of Thomas Young

Returning to Grenoble in 1809, Champollion became a teacher at its new university, where his older colleagues were jealous of his success, even though his salary was far lower. His penury constantly undermined his health, and although he wanted to marry Rosine Blanc, a local girl, her father stubbornly opposed the marriage. Champollion’s research into Coptic and hieroglyphs continued, but was limited by insufficient material and disrupted by the political upheavals in France. Throughout the chaos he tried to continue working and returned to the Rosetta Stone. In November 1814, he finally wrote to London saying that he was confident of reading the entire inscription if only he could be sent what was illegible on his copy. His letter fell into the hands of Thomas Young.

Unknown to Champollion, Young was his greatest rival. Seventeen years older than Champollion, he was from a Quaker family from Milverton in Somerset. Gifted in both sciences and languages, Young studied medicine and traveled in Europe as much as was possible during Napoleon’s campaigns. A considerable inheritance from his uncle ensured that he as Arabic, Hebrew, Aramaic, and Persian, any spare time was concentrated on becoming fluent in Coptic, with the help of Dom Raphaël and also Yuhanna Chiftichi the Coptic priest of the church of Saint-Roch in the rue Saint-Honoré.

Champollion also examined Egyptian papyri with hieratic writing, believing that hieratic was the same as the demotic on the Rosetta Stone. In fact, hieroglyphs were a type of formal writing, and hieratic was a more simple, handwritten, cursive type of hieroglyphs. Hieratic writing became very stylized and developed into what is called demotic, which replaced hieratic from around 650 BC. After Alexander the Great invaded Egypt in 332 BC, Greek became the main bureaucratic language. From the subsequent Roman period, the Egyptian language was written using a new script, Coptic, which was a mixture of Greek and demotic letters. Although Arabic became the main language and writing system in Egypt, the Christians continued to speak and write the Coptic language. This succession of different scripts and languages was part of the problem facing scholars, and by the end of 1808 Champollion declared to Jacques-Joseph that he could progress no further with hieroglyphs and that the Rosetta Stone was of no further help.
never suffered financial hardship, nor was he affected by political turmoil. In 1814, Young was given a papyrus from Egypt, written in hieratic, which inspired him to begin research on the Rosetta Stone, which was on display in the British Museum. Initially, he analyzed its demotic inscription, which he termed enchorial, and sent his results to Professor Silvestre de Sacy in Paris, a staunch Royalist who once taught Champollion. Shortly afterwards, Young made some progress with the Rosetta Stone's hieroglyphic text, surpassing anyone else's work, even though much of his analysis would turn out to be incorrect. In his role as foreign secretary of the Royal Society, Young now received Champollion's letter claiming his own virtual success.

The political situation once again touched Champollion with a heavy hand. Having escaped from Elba, Napoleon reached Grenoble on 7 March 1815, where he persuaded Jacques-Joseph to become his secretary. Champollion was presented to Napoleon, who pledged support for his Coptic dictionary and grammar. The emperor and the linguist, the two men who between them, but in such different ways, did the most to establish the study of Egyptology, met for just a few minutes—it was their only meeting.

Jacques-Joseph accompanied Napoleon to Paris, but Champollion remained in Grenoble, the last town in France to offer resistance to the allied forces, where he was forced to run through exploding shells to safeguard the library from fire. It was now that Champollion received a reply from Young, containing little new information, but showing that de Sacy had failed to forward material from Young. After Waterloo and with Louis XVIII back on the throne, the two brothers were regarded as dangerous and lost their university posts, and in March 1816 they were condemned to internal exile in their home town of Figeac. De Sacy now tried to discredit Champollion, warning Young not to trust him with his discoveries in case he claimed them as his own—an unfounded charge frequently used by his detractors.

Only in October 1817 did Champollion dare return to Grenoble, where he became immersed in a project to establish new schools. Unable to work at the university, he accepted a teaching post in the Royal College and at the end of December 1818 finally married Rosine. By now Thomas Young had amassed a huge amount of information on hieroglyphs and succeeded in recognizing the hieroglyphic name Ptolemy on the Rosetta Stone and in working out some of the hieroglyphic alphabet. He published his results at the end of 1819 as a supplement to the *Encyclopaedia Britannica*, far exceeding anything published by Champollion.

In Grenoble, the Ultras (extreme Royalists) were causing much unrest, and Champollion lost his teaching post. During an uprising against the Prefect, Baron d’Haussez, in March 1821, Champollion dared raise the tricolor flag over the citadel with a group of other men, for which he was threatened with trial for treason. Although eventually acquitted, his spirit and health were broken, and he abandoned Grenoble in July, making his way to Paris to be with his brother. By the end of the summer the entire family including his wife moved to the rue Mazarine.

**The breakthrough**

Champollion was now left in peace to rebuild his health and concentrate entirely on ancient Egypt and its writing systems. His deep knowledge of Coptic and his persistence began to bear fruit, and he rapidly overtook Young. Two major events precipitated his progress.

In January 1822 he was given a copy of an inscription from a six-ton obelisk that had recently been transported from Philae in Egypt to the country home of William Bankes in Dorset. From this, he worked out the hieroglyphs of the name “Cleopatra” and began to appreciate the complexities of hieroglyphs when used for the Egyptian language and when spelling out foreign names like Cleopatra and Ptolemy.

Then, on the morning of 14 September 1822, he found further crucial evidence on inscriptions from Abu Simbel and realized that phonetic signs were not just used for foreign names in the Greek and Roman periods, but in earlier Egyptian writing as well.
Hieroglyphs are signs that appear to be mainly pictures of animals, people, plants, and objects, and the earliest scholars believed they contained hidden, mysterious meanings. The main types of signs are pictographs, ideograms, phonetic symbols, and determinatives. The simplest are pictographs, where a word is represented by a single picture, so that a duck means simply “a duck.” In ideograms, a hieroglyphic sign represents an idea, so that “daytime” is shown by a picture of a sun. Phonetic signs represent a particular sound. There were twenty-four representing single consonants, similar to an alphabet. Others represented a combination of two or even three consonants. Decipherment was made more difficult, because a sign could be used in different ways depending on its context. The sign “duck,” for example, can be used as a pictogram meaning “a duck” or an ideogram meaning “son of,” or it can represent the sound “sa.”

Where signs had several meanings, a scribe might add other signs called “determinatives.” They were not pronounced, but gave clues about a word’s meaning, so that a pair of legs in-
The landmarks

1762: A priest, Jean-Jacques Barthélemy, suggests that the oval rings with a bar (cartouches) found in Egyptian hieroglyphic texts could contain royal names or those of gods.

July 1799: In Egypt, a French soldier, D’Hautpoul, recovers the Rosetta Stone with its hieroglyphic, demotic, and Greek inscriptions, from a wall being demolished, and his superior, Lieutenant Pierre François Xavier Bouchard, recognizes its potential importance.

1801: The Stone is taken as spoils of war by the British and displayed at the British Museum the following year.

1802: French orientalist Antoine Isaac Sylvestre de Sacy locates the approximate groups of demotic characters forming the names “Ptolemy” and “Alexander.” Shortly thereafter, his student Johan David Åkerblad, a Swede, identifies all the proper names in the demotic text that are also in the Greek text. He establishes a demotic alphabet of 29 letters, half of which were incorrect, but he fails to recognize that the demotic text also includes ideographic characters.

1805: Champollion starts studying modern Coptic, the pronunciation of which he assumes to be closely related to hieroglyphs. His fluency in Coptic was the main factor in his ability to decipher hieroglyphs.

1819: Thomas Young publishes his idea that, like demotic, the hieroglyphic text also uses phonetic characters for foreign names. He identifies the phonetic characters in the cartouches of Ptolemy and deduces that the neighboring cartouche is of Berenice. However, he erroneously believes that native Egyptian names only use ideographic characters, whereas they use both ideographic and phonetic characters.

1820-22: Based on a numerical count of the Greek words and hieroglyphic characters of the Rosetta Stone, Champollion finds that the relationship is neither consistent with hieroglyphs being used only phonetically nor of their being used only as ideograms. He concludes that these two uses are combined. He recognizes the name Ptolemy in a demotic papyrus and suspects another name is Cleopatra. By attempting to reconstruct the hieroglyphs from the demotic characters, he arrives at a hypothetical hieroglyphic version of Cleopatra, which he is able to confirm thanks to a cartouche from an obelisk from Philae.

The eureka moment

14 September 1822: 23 years after the discovery of the Rosetta Stone, Champollion examines a cartouche he has never seen before on a drawing from the Abu Simbel temple. From cartouches of Ptolemy (which read Ptolmys), he already knows that the last two symbols represent “ss.” His knowledge of Coptic enables him to deduce that the first symbol, representing the sun, is “Ra,” and he guesses the middle sign to be “m.” By inserting vowels, the Abu Simbel cartouche contains the name “Ramses” (Ramesses). With mounting excitement, he searches the drawings for another cartouche: he finds one that has an “s” and the likely “m.” He knows the ibis sign is the symbol of the god Thoth, so the cartouche reads “Thotmes,” a Pharaoh better known today as Tuthmosis. Everything falls into place, he has cracked the code!
latest results and thinking. He was warmly congratulated by those present, including Thomas Young who by sheer coincidence was in Paris for a short visit and had witnessed his rival's triumph. Despite friendly exchanges of correspondence, Young spent the rest of his life, until his death in 1829, bickering over who was responsible for identifying a few letters, not helped by Champollion giving him scant acknowledgement in his publications and highlighting where Young had gone wrong.

An Italian interlude

In 1824, Champollion was sent to Turin in Italy to study their newly acquired Egyptian collection. He surged ahead with translations of hieroglyphic texts, each one providing more startling discoveries than the last, including the disturbing revelation that pharaohs ruled Egypt long before the date of Creation calculated from Biblical texts. His earliest dreams had come true—he now had access to completely new evidence for the earliest history of mankind and maybe Creation itself. From now on, the Rosetta Stone really was of no further use. After some months, Champollion traveled elsewhere in Italy, making one detour to Livorno to examine a collection of Egyptian antiquities that was being sold by Henry Salt, British Consul in Egypt. Champollion was astounded by its quality, immediately writing to his brother that it must be purchased by France. In November 1825 Champollion returned to France and was informed a few weeks later that the king had allocated him finance to return to Livorno to study the Salt collection. News soon reached him there that the collection was definitely being purchased and that he should prepare it for shipment to Paris, and in May 1826 he was appointed curator of a new Egypt section at the King Charles X Museum within the Louvre Palace.

While waiting for the ship to arrive to transport the collection to Paris, Champollion became acquainted with Ippolito Rosellini, Professor of Oriental Languages at Pisa, and for several weeks they worked closely together, with Champollion teaching Rosellini about hieroglyphs and Egypt. By November 1826, Champollion was back in Paris, where he ran into opposition over the new exhibits at the museum. At the same time he was putting together a joint French-Tuscan expedition to Egypt, with Rosellini as his assistant, and he set sail from Toulon on 31 July 1828, almost exactly three decades after Napoleon had sailed from the same port with his own expedition.

The Egypt expedition

To Champollion, being in Egypt was almost like coming home, as he took so readily to its life and climate, and his indifferent health improved greatly. The plan was to go from Alexandria
to Cairo, then as far as the second cataract at Abu Simbel, assessing and identifying sites as they traveled upstream. On the return journey, the expedition members, mainly artists and draftsmen, would undertake the detailed recording. Some sites took longer to assess than planned, but they were horrified to discover that countless significant monuments recorded by Napoleon’s savants had recently been destroyed for building works or burnt in lime kilns. As for the pioneering work of the savants, Champollion complained that their copies of hieroglyphs were often inaccurate.

By the end of 1828, Champollion was suffering bouts of what was described as gout, which periodically hampered his work. In early January 1829, the expedition members were back at Abu Simbel, with its two rock-cut temples of the pharaoh Ramesses II overlooking the River Nile, an area that was destroyed by the building of Lake Nasser in the 1960s, though these two temples were rescued. Discovered in 1813, desert sand still buried the façade of the monument, and inside the temples the temperature was like a furnace. By March, the expedition had reached Thebes and spent several weeks on the west bank of the Nile, taking up residence in the tomb of the pharaoh Ramesses IV in the Valley of the Kings. They later concentrated on the temples on the east bank at Luxor and Karnak. In front of the magnificent Luxor temple were two obelisks, and Champollion wrote to Jacques-Joseph that the French government should consider removing one to Paris. Back at Cairo once more, Champollion was shocked to learn that his adversary Thomas Young had died a few months previously, while they were in the Valley of the Kings. His ship was then delayed, so that Champollion did not return to France until 23 December 1829, followed by a month of quarantine. He was terrified of further illness if he went back to damp, cold Paris, but in March he did return, having learned of opposition towards him and rumors of falsifying the evidence about deciphering hieroglyphs.

Final words
In the second half of 1830, France experienced revolution, and in late July thousands of armed citizens broke into the Louvre Museum and stole numerous objects from Champollion’s Egyptian galleries, some of which he had only just brought back. Charles X fled to England, but fortunately the

The keys of Egypt: Jean-François Champollion – Adkins and Adkins

**Place des Écritures at Figeac,** Champollion’s birthplace, in the Lot department. On the ground is an enlarged 14×7-m copy of the Rosetta Stone in black granite from Zimbabwe, by American conceptual artist Joseph Kosuth (2000). © Hervé Champollion/akg-images.

**Champollion’s tomb** at the Père-Lachaise cemetery, Paris. © Roy and Lesley Adkins.

**Papyrus from the Book of the Dead of Tchahaplimou, Superior of the Astronomers of Amun.** Ptolemaic period, 500-100 BC. Musée du Louvre, Paris. © RMN–Grand Palais/Franck Raux.
new king Louis-Philippe was sympathetic towards Champollion’s work, and in March he was appointed as Professor at the College of France. In May, he began his new university course, but his deteriorating health forced him to break off and retreat to Figeac, where he was left in peace to work on his hieroglyphic grammar. His health started to improve, and he reckoned he needed one more month to complete the grammar, but Jacques-Joseph insisted he was needed in Paris. He arrived there on 28 November and resumed his university course to great acclaim a few days later. In mid-December he suffered a stroke and had trouble writing. He was gradually improving, but on 12 January 1832 he collapsed and could barely talk. By the end of February he was drifting in and out of consciousness, and on 4 March he died, at the age of forty-one. Two days later his body was taken to the nearby church of Saint-Roch, where he had learned Coptic from the priest, and a massive funeral cortège set off for the Père-Lachaise cemetery. While Jacques-Joseph embarked on preparing his papers for publication, including his Egyptian grammar and a dictionary, the tragic early death of Champollion did not soften the attitude of some of his opponents, who continued to deny the value of his work. Other scholars such as Richard Lepsius in Germany, Samuel Birch in England, Edward Hincks in Ireland, and Emmanuel de Rougé in France acknowledged his vast achievements and took steps to build upon them, expanding the understanding of hieroglyphic texts and the secrets they contain. Today Champollion’s work is universally recognized. By discovering the keys to the ancient Egyptian language, he unlocked the chronicles of a complete civilization.

Further reading


Les clés de l’Égypte : Jean-François Champollion

Jean-François Champollion naquit le 23 décembre 1790 à Figeac, dans le Lot. En 1801, sa famille l’envoya chez son frère Jacques-Joseph, à Grenoble, où il se prit de passion pour les langues anciennes, l’Égypte et ses hiéroglyphes. À 16 ans, il part deux ans étudier à Paris, puis retourne à Grenoble où il enseigne à l’Université nouvellement créée. Il y poursuit ses études sur les hiéroglyphes, mais ses progrès sont entravés par la piètre qualité des copies disponibles de la Pierre de Rosette. Celle-ci avait été découverte au cours de la Campagne d’Égypte de Napoléon, mais avait dû être cédée aux Anglais. En quête d’une copie plus exacte, Champollion entra en contact avec Thomas Young à Londres, sans savoir qu’il s’agissait de celui qui allait devenir son grand rival dans le déchiffrage des hiéroglyphes. Champollion, qui avait soutenu publiquement Napoléon échappé de l’île d’Elbe, perdit son poste à Grenoble et se vit exilé à Figeac. Lorsqu’enfin il put retourner à Grenoble, les désordres politiques l’en chassèrent en 1821 et il partit pour Paris. Malgré une santé chancelante, il consacra toute son énergie à l’examen des hiéroglyphes. L’année 1822 fut le grand tournant où Champollion perça enfin leur mystère et réussit à déchiffrer un nombre croissant de textes. Devenu conservateur des collections égyptiennes du Louvre, il se partagea entre ses responsabilités au musée et des séjours en Italie, avant de prendre la tête d’une expédition franco-toscane en Égypte, où il fit faire des avancées considérables à l’égyptolistique. De retour à Paris en 1830 pour y enseigner ses découvertes au Collège de France, la maladie l’obligea bientôt à se réfugier à Figeac, où il travailla à sa Grammaire Égyptienne. Une dernière fois il se rendit à Paris, où il fut victime d’un accident vasculaire cérébral et s’éteignit le 4 mars 1832, âgé seulement de 41 ans.
Page blanche pour conserver, en pdf,
la présentation,
en vraies doubles,
de la maquette finale
The time draws nigh when we shall feel that to truly destroy England we must seize Egypt.” Thus wrote Napoleon Bonaparte to the French government one year before his army entered Alexandria in July 1798. Marked by battles won and lost, revolts and reprisals, propaganda and backlashes, the French occupation of Egypt lasted but three years. What remains of its martial ambitions may perhaps be traced in the pages of military manuals, but its legacy is not the work of men of war, but of doctors, scholars, and scientists—the Description of Egypt—a multivolume work on Egyptian antiquities, flora and fauna, geology, climate, diseases, town planning, politics, and economics. Bonaparte himself supervised the medical and sanitary preparations for his Campaign of Egypt. On the ground, his medical men strove to overcome a host of difficulties that beset the troops: dehydration, cholera, ophthalmia, plague, and more. By setting up hospitals and lazarettos (quarantine stations), studying diseases, and implementing hygienic initiatives, the French medical corps enjoyed some measure of success. At the newly created Institut d’Égypte in Cairo, presided over by the mathematician Gaspard Monge, French scientists and doctors held scientific meetings and published their findings. Meanwhile, subject to increasing pressure from British and Ottoman forces, the French military capitulated at Alexandria in August 1801 and were expelled. Muhammad Ali, the “Father of Modern Egypt,” took power and for this he recruited doctors and medical instructors from France to help modernize health care in Egypt. One such, Antoine Barthélémy Clot, a doctor and surgeon in Marseille, embarked in 1825 for Egypt, where he spent over a quarter of a century. Soon after his arrival he cured Muhammad Ali of gastroenteritis, became his personal physician, and later was appointed chief health care administrator, and so by creating medical schools and hospitals laid the foundations of modern medical instruction and care in Egypt.

Medicographia. 2013;35:124-133 (see French abstract on page 133)
French doctors in Egypt with Napoleon – Régnier
The Egypt Napoleon Bonaparte invaded in 1798 had been part of the Ottoman Empire for nearly three hundred years. The Ottomans ruled through the Mamluks, dynasties of emancipated slaves captured in Turkestan, southern Russia, and eastern Europe (Georgians, Slavs, Greeks). The Mamluks had held sway over the country since the 13th century, their power rooted in an elaborate military organization and in control of the spice trade with the European powers.

**Dream and substance in the Orient: the French in Egypt**

Bonaparte prepared the Campaign of Egypt in the utmost secrecy (in relation to the British). The Directory (a body of five directors that held executive power) made available to him—a young general not yet 30 years old—considerable wherewithal: 355 ships manned by 16,000 sailors to transport 38,000 men (and 340 women). In part perhaps because, as has often been remarked, the Directory was not averse to a lengthy absence of the Emperor from French soil: “He is gone, the saber is receding,” proclaimed the parliamentary deputy Paul Barras when the squadron left Toulon in May 1798.1,2

The campaign was not only military, since 167 scientists and artists embarked with their instruments and books. The expedition was designed to ensure an enduring French presence along the banks of the Nile,3,4 and Arab-speaking savants and printers spread French culture throughout Egypt by printing bilingual books (the Arabic characters had been recovered from the presses of the Vatican). French scientists and doctors reported that health care organization in Egypt was woeful, with people in thrall to charlatans and ignorant barber-surgeons. Recent historical studies though tend to belie these peremptory assertions by late 18th-century Westerners.

Egyptian doctors, surgeons, midwives, oculists, bone-setters, and barber-surgeons were organized in guilds, and—at least the most erudite among them—referred to the same principles of humoral medicine as their European counterparts. This is borne out by the fact that 78% of the remedies employed in Egypt were identical to those administered in France in the same indications, including bloodletting and cupping therapy. In Egypt, the doctor was a learned man who studied the great medical texts of the ancient world and of the Arab tradition, as well as astronomy, physics, and botany. The training and studies for the diploma of doctor were, it is true, more theoretical than those required of French doctors, who had already turned to clinical anatomy following the wide-ranging reforms of medical teaching implemented in Revolutionary France. Medical practice, though, was the work of Egyptian artisans whose training was more rudimentary, but whose deftness was often recognized, notably in the case of oculists. Alongside this decentralized medical organization, healers, exorcists, and magicians were tolerated because of their substantial contribution to the healing of patients.3,5 Such was the state of medical education and care in Ottoman Egypt when the French entered Alexandria in the summer of 1798.

Influenced by Count Volney’s accounts of his contemporary travels in the Middle East, Bonaparte admired the civilization of ancient Egypt and had even once considered putting himself at the service of the Sublime (or Ottoman) Porte (a reference to a gateway used as a place of assembly at the Topkapi Palace in Istanbul, and as such a metonym for the government of the Ottoman Empire). Inspired by Enlightenment philosophy, the impetuous general dreamed of bringing to the peoples of the Orient the principles of the French Revolution so as to restore the lost grandeur of the ancient civilizations. Like the French government and its diplomats, the young Bonaparte thought that the Sultan of the Ottoman Empire, Selim III, whose artillery and fleet the French were reorganizing, would look favorably upon the reining in of the Mamluks, Egypt’s de facto rulers.

Bonaparte himself oversaw the health care organization of the expedition by assuming that one man in ten risked falling ill, one in 25 would likely be wounded, and that well-planned supplies of medical remedies would be necessary. In March 1798, Bonaparte ordered Simon de Sucy, the chief paymaster of the army in Egypt, to take as many surgeons and doctors as possible, either from the army in Italy or from wherever he found himself, because “you will never have too many [...] procure two or three hundred nurses, eight or ten good hospital directors.”

In all, Sucy managed to find 168 “second-class doctors” (who, after passing certain examinations, had completed an apprenticeship of six years with a doctor or of five years in a hospital or three years’ study at a medical school), 108 of whom were surgeons (young and unversed), that is one doctor for 1530 soldiers and one surgeon for 350. Bonaparte’s chief...
medical officer, René-Nicolas Dufriche Desgenettes, invited his doctors to familiarize themselves with the diseases encountered in Egypt by reading Count Volney’s book on his travels in Syria and Egypt. Also taken along were 190 pharmacists, 142 hospital administrators, and 9 staff to run the lazarettos for epidemiological surveillance. Each military division had an ambulance, wound dressing equipment, surgical instruments, and medicines. The vessels of Bonaparte’s fleet were equipped with a sick bay and three were fitted out as floating hospitals. Some ships though never reached their destination. Le Patriote struck a reef west of Alexandria and sank, taking with it flexible stretchers, boxes of surgical instruments, and other equipment. The Bienfaisance too foundered with its boxes of surgical dressings and scientific apparatus.2,3,8,9

“The most virtuous man I ever knew”
Such was Bonaparte’s opinion of his Chief Surgeon, Dominique-Jean Larrey. During the Italian Campaign, a year before the invasion of Egypt, Bonaparte said to Larrey “Your work is one of the greatest creations of our century, and alone suffices to secure your reputation.” Later Napoleon, by then Emperor, also said “If the (French) army ever erects a monument to express its gratitude, it should do so in honor of Larrey.”

Larrey’s reputation knew no borders, and as Napoleon’s reign was nearing its end, at the Battle of Waterloo (1815), the Duke of Wellington ordered his soldiers not to aim in the direction of Larrey, who was working under fire to perform amputations, dress wounds, and evacuate the injured. The Duke doffed his hat and, in response to the enquiry “Who are you saluting?” pointed at Larrey with his sword saying “I salute the courage and devotion of an age that is no longer ours.”

Such was the measure of Dominique-Jean Larrey.

Larrey revolutionized battlefield medicine. He devised and developed the famous ambulances volantes (literally “flying ambulances”), field ambulances for rapid collection and evacuation of the sick and wounded, even in the heat of battle. These were purpose-built carriages, horse-drawn vehicles, or, in the desert, dromedaries bearing wooden stretcher-like compartments. This in an era when the wounded, if not simply abandoned to their fate, were tipped pell-mell onto local bullock carts for transportation.

Larrey also operated a system of triage, treating casualties according to the severity of their wounds and the urgency of the need for medical care, regardless of rank, friend and foe alike.

Vomiting root, maggots, and mercy killings
On arrival in Egypt Bonaparte ordered his staff to replace his soldiers’ uniform, which he deemed unsuited to the climate, by loose-fitting garments in white cotton, akin to those worn by the Mamluks. In the event, only the regiments mounted on dromedaries were kitted out in this way.
hydration and administration of quince jelly combined with the South American vomiting root (ipecacuanha or ipecac root, from the flowering plant Carapichea ipecacuanha). Ophthalmia (inflammation of the eye), aggravated by the blazing sunlight and windborne sand, was either gonococcal or chlamydial (caused by the Gram-negative bacterium Chlamydia trachomatis), in which case it came to be known as Egyptian ophthalmia (trachoma). In twenty-four hours the cornea was eroded, resulting in irreversible lesions. Desgenettes reported that one third of the population of Cairo was affected, writing “No other town has as many blind people.” Larrey wrote a remarkable description of ophthalmia, and advocated treatment by direct application to the eye of a poultice or cataplasm of aluminum sulfite and camphor.

The French largely escaped the ravages of smallpox, but 150 000 inhabitants of Cairo fell victim in 1801. Malaria was treated by the massive and haphazard administration of quinine (from the bark of the cinchona tree, Cinchona officinalis), which yielded spectacular results. Syphilis and gonorrhea were faithful camp followers throughout the campaign, and in a brutal, and vain, attempt to control their spread four hundred prostitutes were decapitated. Two venereal disease hospitals were opened, one in Cairo the other in Jaffa.

Surgeons made valuable observations of deep wounds made by the keen-edged Damascus steel of the Mamluks’ curved sabers. If a soldier’s injuries did not necessitate amputation, and he was not infected by tetanus, which was always fatal, blowfly maggots were applied to cuts because they release allantoin, which promotes tissue healing.2,8-12

Yet despite the doctors’ preparations, what afflicted the Egyptian Campaign above all was pestilence, the bubonic plague. When the first cases were reported in December 1798 at the medical hospital in Alexandria, drastic quarantine measures and disinfection procedures were put in place. Despite alarming rumors of an epidemic in Syria, 12 000 French troops left for Galilee in February of 1799, and by March 300 stricken soldiers were crammed into the Pesthouse of Jaffa. The doctors and surgeons there vied with one another in boldness by inoculating themselves with pus from buboes, to prove that the pestilence was not contagious. And they were forbidden from uttering the very name of the disease in front of the soldiers.

At the siege of Saint Jean d’Acre from March to May, 500 men died in combat, 2000 wounded were treated and evacuated by sea and across the desert, and half of the 2000 sick had the plague. Treatments at the time were pitiable: incision of the buboes, scarification of the skin on the neck, administration of acidic drinks. When asked by Bonaparte to administer overdoses of opium to suffering soldiers, Desgenettes refused, but Claude Royer, the chief pharmacist, complied. It is believed there were thirty or so mercy killings of plague victims unfit to be moved; the British, who made political hay of the incident, spoke of 500.2,3, 8,12

**The new science of Egyptology**

Military ups and downs and the ravages of unexpected diseases turned Napoleon’s expedition into a medical and health disaster. Among the 38 000 soldiers mobilized, Desgenettes counted 4758 who died in action and 4157 who succumbed...
to disease, 1689 of them to the plague. Rare it was at the
time that men killed in battle outnumbered the victims of dis-
ease, and this, it may be said, bears witness to the effective-
ness of the health measures put in place.\textsuperscript{2,12} At the hospital in
Cairo, Desgenettes opened a school of medicine and phar-
macy. Lacking health and sanitary backup after the British
destroyed the French fleet at Aboukir on 1 August 1798, the
hospital staff suffered increasing shortages of medicines and
surgical instruments, whence their attempts to put in place
a lasting health care organization by using local human and
material resources. French doctors imposed

\textit{Desgenettes, Chief Medical Officer during
Napoleon’s Egyptian Campaign, inoculating him-
self with the plague. Color engraving, author un-
known. Château de Malmaison et Bois-Préau.}
© RMN–Grand Palais/Daniel Arnaudet.

collective (and often unpopular) hygienic mea-
sures, such as the setting up of town coun-
cils with powers in matters of sanitation, ban-
nings burials within towns, removal of stagnant
water, and organized refuse collections.\textsuperscript{2,3,8}

In August 1798, Bonaparte founded in Cairo
the \textit{Institut d’Égypte}, which was presided over
by the mathematician Gaspard Monge. The
Institute’s newspaper, the \textit{Courrier de l’Égypte},
was copyedited by Joseph Fourier, who is
credited with discovering what we now call
the greenhouse effect, and who is associat-
ed with the eponymous series, transforms,
French doctors in Egypt with Napoleon – Régnier

and law he devised. Dedicated to Bonaparte and two of his generals, the three-volume *La Décade Égyptienne* reported the sessions of the *Institut d’Égypte* and the communications of the members of the arts and sciences commission, notably articles on diseases observed in Egypt, like ophthalmia, elephantiasis, and filariasis, the plague, and the relations between the Nile floods and the occurrence of epidemics. Chief pharmacist Claude Royer published there a complete review of the pharmacopeia common in Egypt.

In addition to conducting the first forensic examinations of Egyptian mummies, Desgenettes published a *Medical Topography of Egypt*, in which he recounted how it was the custom for wet nurses to ingest a remedy intended for the infants they suckled, anticipating its absorption with breast milk.

Appointed supreme commander of the armies in Egypt, after the departure of Bonaparte on 22 August 1799, General Jean-Baptiste Kléber decided to collect and publish all the observations of the expedition’s scientists in a monumental work entitled the *Description de l’Égypte*. Published between 1809 and 1828, this limited edition of 1000 copies, 200 of them reserved for the Emperor, comprised nine volumes of text, ten volumes of plates containing 974 engravings, and a cartographic atlas.

The *Description de l’Égypte* contained plates 1 by 0.81 meters, and was delivered by the imperial (and later royal) printing office with its very own cabinet. Thanks to the exceptional scientific output of the expedition’s savants in many fields of learning—archeology and ancient history, botany, zoology, medicine, epidemiology, geography, and mineralogy—European fascination with all things of the land of the Pharaohs, its Egyptomania, had now become the new science of Egyptology.

**Aftermath and legacy**

When the French left Egypt in September 1801 after a series of defeats against the Ottoman Turks and the British, there had been too little time for their praiseworthy attempts at modernization to take root throughout the country. But they had laid the groundwork for the changes and reforms implemented by Muhammad Ali, a commander in the Ottoman military.

Muhammad Ali was born in Kavala in eastern Macedonia to Albanian parents. Contemporary witnesses reported that he spoke only Albanian fluently, but was competent in Turkish, the official language of his court, rather than Arabic. He arrived in Alexandria in the spring of 1801 just after the departure of the French. Through skilled political maneuvering, and with the backing of the Ottoman Sultan, Selim III, he managed...
Antoine Barthélémy Clot was but five years old when Napoleon’s Campaign of Egypt began, yet he was later to play a key role in its aftermath and in the birth of modern medicine in Egypt. Born in 1793 in Grenoble, Clot successively qualified as an assistant surgeon, barber-surgeon, a so-called second-class doctor, and lastly a fully-fledged doctor of medicine in Montpellier in 1820. Three years later, he completed a doctorate in surgery in Marseille and then signed a five-year contract to become doctor and surgeon in chief of the army of Muhammad Ali, seen by many Egyptians as the “Father of Modern Egypt.”

Clot sailed for Alexandria early in 1825, with his library, surgical instruments, and a human skeleton, in the company of twenty doctors placed under his authority. On arrival in Cairo, he was called upon to treat Muhammad Ali who was suffering from gastroenteritis. Shaped by the new French medicine, skilled too in the art of surgery, Clot stayed on for a quarter of a century. He sought not to transpose the French model to Egypt, but rather to adapt it to the epidemiological and cultural realities of his adopted homeland.

Backed by Muhammad Ali, who had become his friend, the unflagging Dr Clot laid the foundations of modern medicine in Egypt. He organized military medicine by recruiting overseas doctors, founded a huge hospital and school of medicine and pharmacy for the military and civilians at Abu Zaabal (near Cairo), where a library, a botanical garden, and a natural history exhibition room were created, and started free medical consultations in Cairo and Alexandria. He set up an advisory body for epidemiological surveillance, put in place in the main towns a network of small hospitals manned by a doctor and a pharmacist, opened a school of midwifery where the courses were given in Arabic by a midwife who had qualified in Paris, and helped expand smallpox vaccination, which was made compulsory in 1846. Lastly, he organized a medical and sanitary department to oversee work in the provinces, such as draining pools of foul water, destroying refuse, and monitoring of industries that posed health hazards. The school of medicine at Abu Zaabal never became a medical faculty, but awarded diplomas of second-class doctor. The subjects taught, the length of the course (six years), the clinical examination at the patient’s bedside, the text books, all were similar to those used in France. To encourage acceptance of the practice of anatomical dissection, Clot used non-Muslim cadavers. General teaching was done in Arabic and the medical courses were taught in French (with an interpreter present).

The student reading list included 54 reference works, 31 of them on French medicine, most of which Clot had translated into Arabic, thereby creating an Arabic vocabulary of modern medical terms. Clot himself wrote eight works, notably on the plague, ophthalmia, vaccination, and cholera. For his deeds during the 1831 cholera outbreak (35 000 deaths), Clot was rewarded with the courtesy title of bey (a provincial governor in the Ottoman Empire). Thereafter he was known as Clot-Bey, and wore a robe and turban. In 1837, the military hospital of Abu Zaabal was transferred to Cairo and became the School of Medicine.

On the death of his protector Muhammad Ali in 1849, Clot-Bey left Egypt, but returned in 1854 to take up the position of President of the Health Commission and Inspector General of the Department of Health. During his four-year stay, Clot-Bey ran “his” school of medicine, which after he returned to France continued to operate on the lines of the original until 1885.

Clot-Bey was elected as a member of the learned society the Académie de Marseille, received numerous French and foreign decorations, and was a member of several societies of medicine and of surgery. For his tomb in the Saint-Pierre Cemetery in Marseille, Clot-Bey chose the inscription Inter infideles fidelis, Believer among infidels.
Over the two centuries following Bonaparte’s 1798 invasion of Egypt, the French-language press there counted nigh on 500 titles, twenty or so devoted to medicine and pharmacy. The highpoint was in the mid-19th century, notably in the medical field. From its foundation in 1866, the Société Médico-Chirurgicale d’Alexandrie (Égypte) published reports on the state of health of the Egyptians and on the principal diseases that afflicted them, like dysentery and liver abscesses. The Conseil Sanitaire, Maritime et Quarantenaire, a public health body founded in 1850, inventoried epidemic diseases, notably among pilgrims on their way to Mecca, in its Bulletin Quarantenaire Hebdomadaire published in Alexandria. The Société Médicale du Caire issued a bulletin under the direction of Georges Zancarol, the head doctor of the Greek Hospital in Alexandria and a member of the Société Médicale des Hôpitaux de Paris.

Over the first few decades of the 20th century, French-language medical journals in Egypt proliferated: Annuaire Médical Égyptien, Bulletin de la Société Internationale de Médecine du Caire and its reports, Presse Médicale d’Égypte, Bulletin Médical d’Égypte, the magazine Santé for the general reader, Revue Médicale d’Égypte and Revue Médicale de l’Orient, Pratique Médicale, and Courrier Médical d’Égypte. Léon Hébert imposed the French language on the pharmacists of Egypt through his Bulletin Pharmaceutique (1900), then the Mois Pharmaceutique Médical, and finally the Bulletin Pharmaceutique d’Égypte in 1923. The last French-language medical journal was the quarterly Médecine d’Égypte, which was launched in 1952 and ceased publication in 1986.

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Au cours du XVIIe siècle, les échanges se multiplièrent entre les ports français de la Méditerranée et l’Égypte alors sous la tutelle de l’empire ottoman par Mamelouks interposés ; il s’agissait d’échanges commerciaux principalement et de relations de voyage. Le grand choc fut l’expédition d’Égypte imaginée à plusieurs reprises par les rois de France et mise en œuvre par le Directoire, en 1798, sous l’autorité du général Bonaparte. Outre ses objectifs politico-militaires, cette expédition est animée d’une grande ambition scientifique. Prolongeant l’esprit des Lumières, les savants et les médecins de l’aventure avaient pour mission de dresser un tableau complet des antiquités, de la botanique, de la zoologie, de la géologie, du climat, des maladies, de l’urbanisme, de la situation politique et économique de l’Égypte. Bonaparte avait supervisé lui-même la préparation sanitaire de l’expédition. Le médecin Desgenettes, le chirurgien Larrey, le pharmacien Royer tentèrent de faire face à des situations difficiles : la déshydratation des hommes, le choléra, l’ophthalmie, la peste… Installant des hôpitaux et des lazarets, observant les maladies, prenant des mesures d’hygiène, le corps sanitaire français obtint quelques succès alors que l’opération militaire tournait au désastre. À l’Institut d’Égypte nouvellement créé au Caire, les savants et les médecins français débutèrent leurs séances scientifiques et commencèrent à publier… En 1804, les Mamelouks réduits et le sultan de l’empire ottoman neutralisé, le vice-roi d’Égypte Muhammad Ali commença un long règne de modernisation et de réformes du pays. L’organisation de la médecine militaire et civile, la condition sanitaire de la population firent partie de ses préoccupations. Pour réussir son projet, il fit appel à Antoine Barthélémy Clot, médecin et chirurgien à Marseille, qui demeura 40 ans en Égypte et façonna la médecine de l’Égypte moderne jouant le rôle de ministre de la Santé. L’École de médecine de Clot-Bey se maintint jusqu’en 1885.
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