Abstract

Aim. – Type 2 diabetes mellitus (T2DM) is often associated with chronic kidney disease. For this reason, this article reviews the relationship between treatment of T2DM and renal disease.

Method. – The review presents the recent French data on the management of diabetes in patients with renal impairment, and discusses the implications of renal disease for the treatment of such patients. Prescribing data are presented for various antidiabetic treatments, and the use of the more commonly prescribed medications is discussed with reference to T2DM patients with renal disease.

Results. – In France, it is estimated that 4–5% of the general population has T2DM and that almost 40% of patients with end-stage renal failure have diabetes. Diabetes and renal disease are both risk factors for cardiovascular morbidity and mortality. Glycaemic control is pivotal in T2DM patients for minimizing the risk of vascular complications and hypoglycaemic episodes, particularly in patients with renal disease who also have a higher risk of hypoglycaemia. Whereas poorly controlled glycaemia increases the risk of renal disease and its progression, the risk is diminished in patients treated intensively for diabetes and in those who achieve stable glycaemic control. Intensive multitargeted treatment can also help to decrease cardiovascular morbidity and mortality, especially if started early in patients who have not yet developed macrovascular complications.

Conclusion. – In recent years, considerable improvement has been observed in France regarding the follow-up of diabetic patients. Less extensive, but nonetheless significant, improvement has also been observed in glycaemic control. However, even though treatment decisions generally take renal function into account, some at-risk treatments are often still being used in patients with renal insufficiency.

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Keywords: Diabetes type 2; Antidiabetic treatment; Chronic renal insufficiency; Prevalence; Cardiovascular risk; Glycaemic control; Review

Résumé


Objectif. – Le diabète de type 2 (DT2) est souvent associé à une insuffisance rénale chronique. Cette revue a pour objectif d’étudier les relations entre l’insuffisance rénale et la prise en charge du DT2.

Méthode. – La revue présente des données récentes sur la prise en charge du patient diabétique insuffisant rénal en France et discute les implications de l’insuffisance rénale pour la prise en charge de ces mêmes patients. Les modalités actuelles de prescription des traitements anti-diabétiques sont discutées chez les patients diabétiques à fonction rénale altérée.

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Résultats. – En France, il a été estimé que 4–5% de la population générale souffraient de diabète et que près de 40% des patients atteints d’insuffisance rénale terminale étaient diabétiques. Le diabète et la maladie rénale constituent des facteurs de risque de maladies cardiovasculaires. Un contrôle de l’équilibre glycémique est essentiel chez les patients atteints de DT2, afin d’éviter le risque de complications vasculaires et d’épisodes hypoglycémiques, notamment en cas d’insuffisance rénale. Par ailleurs, une glycémie mal contrôlée est un facteur de risque de progression de la maladie rénale et, inversement, l’apparition et la progression de cette dernière sont ralenties chez les patients traités pour leur diabète de façon intensive et pour lesquels l’équilibre glycémique est maintenu. Un traitement intensif est également bénéfique en termes de réduction de la morbidité et la mortalité cardiovasculaires, particulièrement dans le cas où ce traitement est mis en place à un stade précoce.

Conclusion. – Depuis quelques années, des améliorations importantes du suivi des patients diabétiques ont été réalisées. Des améliorations plus modestes mais significatives ont été observées quant à la prise en charge de l’équilibre glycémique. Cette prise en charge prend en compte généralement la situation rénale des patients mais, elle fait encore souvent appel à des produits qui peuvent présenter des risques en cas d’insuffisance rénale chronique.

Mots clés : Diabète type 2 ; Traitement antidiabétique ; Insuffisance rénale chronique ; Prévalence ; Risque cardiovasculaire ; Équilibre glycémique ; Revue générale

1. Introduction

Type 2 diabetes mellitus (T2DM) is considered a modern-day pandemic, and the number of cases is increasing dramatically each year. According to the World Health Organization (WHO), more than 220 million people worldwide are now known to have the disease. Moreover, it is well recognized that diabetes is often associated with renal disease. On the one hand, diabetes is a well-characterized risk factor for renal disease while, on the other hand, in some individuals, severe renal disease can lead to an increase in blood sugar levels. In addition, diabetes and renal disease are independent risk factors for cardiovascular morbidity and mortality, and the risk is increased when both pathologies are present. For these reasons, the present review focuses on renal disease in patients with T2DM in France, and on the pharmacological management and control of glycaemia in patients with renal insufficiency.

2. Prevalence of diabetes in France

Based on data collected by the French National Sickness Fund, the prevalence of pharmacologically treated diabetes in France was estimated to be 4.4% in 2009, corresponding to 2.9 million individuals [1]. The prevalence increases with age (0.4% in 0–44-year-olds vs 14.8% in ≥ 75-year-olds) and is higher in men than in women (6.3% vs 4.5%, respectively; gender ratio: 1.4). The highest prevalence was found in those aged 75–79 years, with one fifth (19.7%) of men and one seventh (14.2%) of women in this age group receiving treatment for diabetes in 2009 [1]. A similar prevalence rate (4%) was found in the INSTANT study in 2006 [2] and the ObEpi study in 2009 [3]. In the latter study, it was estimated that 5.4% of the adult population were being treated for diabetes, of whom 4.8% had T2DM [3].

Studies of trends in the prevalence of diabetes among subjects covered by the French National Sickness Fund have shown a mean annual increase of 5.7% between 2000 and 2005 [4], and of 4.7% between 2006 and 2009 [1]. Although these increases included all age groups, it was most prominent in patients over 80 years of age, for whom the mean annual increase was more than 6% in men and 5.5% in women [1]. However, the overall increase in the prevalence of diabetes can probably be explained, at least in part, by the ageing of the general population, the increased life-expectancy of diabetic patients and the increasing prevalence of obesity [3].

T2DM accounts for the vast majority of diabetes cases in Western Europe. The 2007 Échantillon national témoins représentatif des personnes diabétiques (ENTRED; National Representative Sample of Diabetic Patients) data, extracted from the national public prescription claims database, revealed that more than 90% (91.9%) of patients prescribed treatments for diabetes had type 2 disease, while 5.6% had type 1 disease and 2.5% could not be classified [5]. In a National Survey on Nutrition, the prevalence of untreated diabetes in those aged 18–74 years in metropolitan France was estimated to be 0.6% in 2006–2007 [6], similar to that found in another large declarative survey, the INSTANT study [2]. Other studies have reported a proportion of untreated diabetes of 3% [7] and 10% [8] of the total diabetic population (0.1–0.5% of the French population).

3. Definition of chronic kidney disease

The definition of renal disease used in France is based on the recommendations of the French National Agency for Accreditation and Evaluation in Healthcare (ANAES) [9] and the French Society of Nephrology (SFN) [10]. Renal function is considered to be chronically altered when abnormalities in markers of renal disease (clinical proteinuria, haematuria, leukocytaire, morphological and histological anomalies, and markers of tubule dysfunction) persist for more than 3 months or the patient has a reduced glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m² [11]. In France, chronic renal disease is diagnosed when the GFR is more or equal to 60 mL/min/1.73 m² with abnormal markers of renal disease, and chronic renal insufficiency when the GFR is less than 60 mL/min/1.73 m². However, the SFN has noted that renal insufficiency is of particular concern in terms of mortality and morbidity when the GFR is less than 45 mL/min/1.73 m².

The GFR is usually determined using equations based on measurements of serum creatinine. In France, the Cockcroft–Gault (CG) equation—GFR (mL/min) = [(140–age (years) × weight (kg)/creatininaemia (µmol/L))] × K, where K = 1.23 for men and 1.04 for women—is still often used to measure GFR, although the Modification of Diet in
Renal Disease (MDRD) equation may also be used, as it is in many other countries [11]. The equation is as follows: 

$$\text{GFR} = \frac{186.3 \times \text{creatininaemia (mg/dL)}^{−1.154} \times \text{age (years)}^{−0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African-American})}{(1.212 \text{ if African-American})} \times (1.212 \text{ if African-American})$$

The isotope dilution mass spectrometry (IDMS)-traceable MDRD equation is: 

$$\text{GFR} = \frac{175 \times \text{creatininaemia (mg/dL)}^{−1.154} \times \text{age (years)}^{−0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African-American})}{(1.212 \text{ if African-American})}$$

Comparison of the CG and MDRD equations in a sample of French patients showed that both formulas lacked precision, although the latter equation resulted in a more precise estimate of GFR, particularly in subjects aged over 65 years and in the obese [body mass index (BMI) > 30 kg/m²] [12]. Thus, from now on and following the implementation of a revised calibration for serum creatinine methods, only the new version of the MDRD equation—the IDMS-traceable MDRD equation—should be used. Recently, however, a third equation, the Chronic Kidney Disease Epidemiology Collaboration (CKD–EPI) equation, has been proposed, and is also based on IDMS [13]. For patients with diabetes, it has been recommended that GFR be estimated with either the CG or, for more accuracy, the MDRD equation [14]. Current information on drug dosages have up to now been largely based on CG estimates of GFR. However, from now on, only the MDRD equation should be used for pharmacokinetic studies and drug dose adjustments [15].

The SFN also emphasizes that the degree of proteinuria is a significant risk factor for progression of chronic kidney disease. Clinical proteinuria can be defined as an albuminurato-creatininuria ratio more than 30 mg/mmol (> 300 mg/g) or a proteinurianto-creatininuria ratio more than 50 mg/mmol (> 500 mg/g), or proteinuria over 24 h more than 0.5 g [10]. The presence of microalbuminuria, defined as either an albuminurianto-creatininuria ratio of 3–30 mg/mmol or urinary albumin excretion rate (UAER) of 30–300 mg/24 h, is associated with an elevated risk of chronic renal disease in type 1 or type 2 diabetics [10].

However, definitions of the various stages of chronic renal disease differ between the French (ANAES) and American (Kidney Disease Outcomes Quality Initiative, KDOQI) recommendations (Table 1) [16]. Thus, to harmonize these international recommendations, the SFN proposed that chronic renal disease be classified into five stages (Table 1). However, the authors of these guidelines also pointed out that, in stage 3 of the classification, the risk of a cardiovascular event or progression to chronic renal insufficiency, or the development of metabolic complications, is increased either by the presence of proteinuria or when GFR is between 30 and 44 mL/min/1.73 m². For this reason, stage 3 (moderate chronic kidney insufficiency) needs to be subdivided into stage 3a, when GFR is 45–59 mL/min/1.73 m², and stage 3b, when GFR is 30–44 mL/min/1.73 m² [10]. Such subdivision of renal disease into stages is consistent with the classification proposed by the UK National Collaborating Centre for Chronic Conditions (NCC-CC) of the National Institute for Health and Clinical Excellence (NICE) [17] (Table 1) and by the Scottish Intercollegiate Guidelines Network on the basis of three studies showing that mortality increases with GFRs less than 45 mL/min/1.73 m² [18–20].

The kidney lesions observed in diabetic patients may be histologically specific (nodular diabetic glomerulosclerosis or hyaline sclerosis) and lead to the identification of so-called ‘diabetic glomerulopathy’. In the absence of biopsy, however, such a diagnosis may be suspected from functional data demonstrating a combination of proteinuria, arterial hypertension and an early reduction of GFR in a patient with long-term diabetes [21]. On the other hand, the KDOQI recommendations refer to ‘diabetic renal disease’ for a diagnosis of renal disease presumably caused by diabetes, and reserve the term ‘diabetic glomerulopathy’ for cases that are histologically proven [16].

4. Diabetes and renal insufficiency

Diabetes is a recognized risk factor for kidney disease, and a significant proportion of patients also present with chronic renal failure [22]. Conversely, in some cases, severe kidney disease can lead to a transitory increase in insulin resistance and a decrease in insulin secretion [23,24]. Poorly controlled glycaemia in patients with diabetes is a risk factor for the development and progression of kidney disease, while diabetes itself is responsible for a large proportion of cases of end-stage renal failure [25,26] and premature death in dialysis patients [27,28]. In addition, the majority of diabetic patients have hypertension: it has been estimated that 49–84% of patients with T2DM in France has an arterial blood pressure more or equal to 130–80 mmHg [5]. Many studies have also demonstrated that arterial hypertension is a risk factor for progression of renal disease in general and in diabetes in particular [29].

In 2008, the French Renal Epidemiology and Information Network (REIN) registry revealed that, of patients with newly diagnosed end-stage renal failure, 26% had hypertensive nephropathy and 23% had diabetic nephropathy [30]. However, 40% of newly dialysed patients had diabetes at the start of dialysis, of which 9% was type 1 [30]. Also, the nephropathy in 59% of dialysis patients with diabetes was considered related to diabetes [30]. The probability of survival in diabetic patients on dialysis or who have received a kidney transplant is closely related to age, being lower in patients who start dialysis later in life [29]; their survival is also significantly shorter compared with dialysis or transplant patients of the same age but without diabetes.

4.1. Prevalence of chronic renal insufficiency in T2DM in France

In the absence of a descriptive observational cohort, no data are currently available on the incidence of renal complications in T2DM in France (excluding end-stage renal disease). In contrast, a relatively clear picture of the prevalence of diabetes by stage of renal insufficiency in this population has emerged. Comparison of data from the 2001 [31] and 2007 [5] ENTRED studies could find no evidence of a change in the distribution of renal disease stages in T2DM over time.
When the SFN 2009 classification (Table 1) was used to stage patients in the ENTRED 2007 study (n = 1543), 43% had stage 1, 35% stage 2, 14% stage 3a, 7% stage 3b, 1% stage 4 and 0% stage 5 disease (using the CG equation). Applying these figures to the total number of T2DM patients treated with medication in France (2.9 million × 91.9% = 2,665,100 people) results in approximately 373,000; 187,000 and 27,000 patients with stages 3a, 3b and 4/5 renal disease, respectively. This represents 587,000 patients overall, demonstrating the importance of this problem.

According to the ENTRED 2007 data, around two-thirds of T2DM patients in France had a reduced GFR, but only 22% had a GFR less than 60 mL/min/1.73 m² and 8% a GFR less than 45 mL/min/1.73 m² (using the CG equation; MDRD corresponding figures are 23% and 6%, respectively). Currently, there are no data on the percentage of patients with chronic renal disease, but with conserved GFR.

4.2. Distribution by age and gender of T2DM patients with renal insufficiency in France

The stage of renal disease in T2DM is closely related to age. An ad hoc analysis of the ENTRED 2007 survey (in metropolitan France) included 1649 T2DM patients (roughly 20% of the overall initial sample of T2DM patients enrolled in the survey) for whom their practitioners had provided the data requested to estimate GFR using the MDRD formula. Patients with a GFR less than 45 mL/min/1.73 m² (stages 3b, 4 and 5) were clearly older than those with less-severe renal disease (74% aged > 75 years vs 5%, 28% and 50% at stages 1, 2 and 3a, respectively). In addition, the proportion of men decreased with the severity of renal disease (63%, 52% and 40% for patients with stages 1, 2 and 3a, respectively, and 34% of those with GFR less than 45 mL/min/1.73 m²).

4.3. Evolution of renal function over time in T2DM patients in France

Analysis of the ENTRED 2007 cohort subpopulation (n = 332), in which patients and their practitioners had agreed to complete a new questionnaire 1 year after the study, showed that renal function had deteriorated (defined as a change in stage) in 15.4% of the patients and improved in 12.3%. Surprisingly, seven patients (95% CI: 2 ± 1.3%) had evolved to end-stage renal failure within this short period of time, although none had severe renal insufficiency according to their initial serum creatinine levels. Although the method of data collection may have introduced some bias (data were collected by practitioners who volunteered to participate), these observations suggest that renal disease evolves in a linear fashion in T2DM patients. However, the rate of deterioration varied according to patients’ characteristics (such as age and duration of diabetes) and the treatments used to protect renal function.

Comparison of the methods used to measure renal function in the ENTRED 2001 and 2007 studies showed that assessment was usually carried out by measuring serum creatinine levels once a year in more than 80% of patients. In contrast, less than one-third of patients had at least one annual albuminuria-to-proteinuria test.

### Table 1

Classification of chronic kidney disease (CKD) according to glomerular filtration rate (GFR).

<table>
<thead>
<tr>
<th>Classification</th>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANAES [9]</td>
<td>1</td>
<td>Chronic renal diseasea</td>
<td>≥ 60</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Moderate CKD</td>
<td>30–59</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Severe CKD</td>
<td>15–29</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>End-stage CKD</td>
<td>&lt; 15 or dialysis</td>
</tr>
<tr>
<td>KDOQI [29]</td>
<td>1</td>
<td>Kidney damageb with normal or ↑ GFR</td>
<td>≥ 90</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Kidney damage with mild or ↑ GFR</td>
<td>60–89</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30–59</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>15–29</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Kidney failure</td>
<td>&lt; 15 or dialysis</td>
</tr>
<tr>
<td>SFN [10]</td>
<td>1</td>
<td>Chronic renal diseasec with normal or ↑ GFR</td>
<td>≥ 90</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Chronic renal diseasec with slightly ↓ GFR</td>
<td>60–89</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Moderate CKD</td>
<td>30–59</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Severe CKD</td>
<td>15–29</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>End-stage CKD</td>
<td>&lt; 15</td>
</tr>
<tr>
<td>NICE [13]</td>
<td>1</td>
<td>GFR normal or ↑, with other evidence of renal disease</td>
<td>≥ 90</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Slightly ↓ GFR with or without evidence of renal disease</td>
<td>60–89</td>
</tr>
<tr>
<td></td>
<td>3a</td>
<td>Moderately ↓ GFR with or without evidence of renal disease</td>
<td>45–59</td>
</tr>
<tr>
<td></td>
<td>3b</td>
<td>Significantly ↓ GFR with or without evidence of renal disease</td>
<td>30–44</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Established renal insufficiency</td>
<td>15–29</td>
</tr>
</tbody>
</table>

a Defined as the persistence for more than 3 months of biological and/or histological and/or morphological renal anomalies.

b Defined as the presence for more than 3 months of histological or blood biological, urinary or morphological anomalies.

c With markers of renal damage (clinical proteinuria, haematuria, leukocyturia), or morphological or histological anomalies, or markers of tubule dysfunction, persisting for more than 3 months.

d Use of the suffix (p) to highlight the presence of proteinuria when renal disease is stable (recommendation R20).
measurement. However, clear improvements in such monitoring practices were seen between 2001 and 2007 [32].

5. Diabetes and renal insufficiency as risk factors of cardiovascular morbidity and mortality

In T2DM, nephropathy is a progressive disease associated with an elevated cardiovascular (CV) risk [33,34]. In the United Kingdom Prospective Diabetes Study (UKPDS), the progression of nephropathy, 10-year survival, and risk of CV and all-causes death were measured in a cohort of 597 patients with recently diagnosed T2DM [35,36]. The annual rates of progression were 2.8% for progression from microalbuminuria to proteinuria, and 2.3% for progression from proteinuria to chronic renal failure. Indeed, all prospective studies to date have produced consistent results, demonstrating that nephropathy is associated with an increased CV risk, with a positive correlation between severity of renal disease and risk of CV morbidity and mortality.

In the Wisconsin study [37], a cohort of 840 patients with T2DM was followed over a 12-year period, during which 264 CV-related deaths were documented. The relative risk (RR) for coronary death was 1.96 [1.42–2.72] in patients with microalbuminuria, increasing to 2.73 [1.95–3.81] in patients with proteinuria, while the RR for fatal stroke was 2.20 [1.29–3.75] in patients with microalbuminuria and 2.33 [1.28–4.24] in those with proteinuria. Although the RR for all-causes death was 1.68 [1.35–2.09] in patients with microalbuminuria, increasing to 2.47 [1.97–3.10] in patients with proteinuria, the RR for CV-related death was 8.71 [4.95–15.31] in patients with both proteinuria and raised plasma creatinine (≥176 μmol/L).

In the HOPE study [38], 3498 T2DM patients were followed for a median of 4.5 years. Microalbuminuria was present in 32.6% (n = 1140) at baseline. The adjusted RR in T2DM patients with microalbuminuria compared with those with a normal UAE was 1.97 [1.68–2.31] for any major CV events, 2.15 [1.78–2.60] for death from all causes and 3.70 [2.64–5.17] for heart failure hospitalization.

In the UKPDS [35,36], the increase in risk of CV-related and all-cause death paralleled the severity of renal impairment. A positive trend was found in the association between the risk of CV-related death and severity of nephropathy (P < 0.0001). The associated annual risk of CV-related death was 0.7% in patients with normal renal function and 2% if microalbuminuria was present, increasing to 3.5% in patients with proteinuria and reaching 12.1% in patients with elevated plasma creatinine (≥175 μmol/L) or on dialysis.

Recent results from the Fenofibrate Intervention and Event-Lowering in Diabetes (FIELD) study [39] have provided additional information on T2DM patients with low CV risk and at an early stage of renal impairment. Patients were stratified into three groups according to basal estimated GFR (eGFR; ≥ 90, 60–89 and 30–59 mL/min/1.73 m², respectively). After a 5-year follow-up, CV risk was increased by 14% in patients with near-normal renal function (eGFR 60–89), and by 59% in patients with renal dysfunction (eGFR 30–59) compared with patients with normal eGFR at inclusion (≥ 90 mL/min/1.73 m²; multivariate-adjusted P < 0.001). Moreover, increased UAE was independently associated with increased CV risk. The RR of CV events increased from 1.25 to 1.94% (P = 0.001) at the microalbuminuria stage, and from 1.1 to 2.3% when proteinuria was present (P = 0.001).

Thus, in T2DM patients, the extent of renal impairment is independently associated with the progression of nephropathy to chronic renal failure, and with a greater risk of death and CV complications. The prevention of progression of renal impairment is therefore crucial to the prevention of cardiovascular risk and early mortality in patients with T2D.

6. Glycaemic control in T2DM patients with renal impairment

Tight glycaemic control can decrease the incidence of cardiovascular morbidity. A meta-analysis of five randomized studies [UKPDS, PROActive, Action to Control Cardiovascular Risk in Diabetes (ACCORD), ADVANCE and the Veterans Affairs Diabetes Trial (VADT)], involving a total of 33,040 T2DM patients followed for an average of 5 years, showed that a reduction in glycosylated haemoglobin (HbA1c) of 0.9 resulted in a lower incidence of coronary events, but with no significant difference in all-cause mortality [40]. In addition, three major interventional studies have also shown that better control of glycaemia can reduce the incidence of microalbuminuria and progression towards macroalbuminuria in T2DM patients [41–45].

7. Antidiabetic treatments in diabetic patients with renal insufficiency

Diabetic patients with renal insufficiency have a considerably higher risk of developing hypoglycaemia than those without it for two reasons: (i) clearance of insulin and certain oral treatments such as sulphonylureas is reduced; and (ii) renal neoglucogenesis is greatly reduced. Some antidiabetic drugs in themselves also bring a high risk of hypoglycaemia, particularly for patients with renal disease. For this reason, it appears to be necessary to adapt treatment dosages and to monitor capillary blood glucose frequently in these patients.

Many antidiabetic treatments are contraindicated or require dose adjustments in patients with renal insufficiency (Table 2), although the information given in the approved prescribing data sheet varies among drugs and is not always clear. Official indications (as noted by the Agence française de sécurité sanitaire des produits de santé, French Agency for the Safety of Health Products) for antidiabetic drugs in relation to the stage of renal disease are presented in Table 2, and are clearly different from those in the KDOQI guidelines [16]. Furthermore, the heterogeneity of the available formulations in the French guidelines results in a number of practical difficulties for the general practitioners (GPs) who prescribe these drugs.

Glipizide, glimepiride and gliclazide are contraindicated in patients with severe renal insufficiency (defined, at least in the case of some generics, as a creatinine clearance less than 30 mL/min), and precautions need to be taken when using these.
Table 2
Indications of hypoglycaemic drugs according to stage of renal disease in France (from the French Agency for the Safety of Health Products).

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Stage 3 (moderate disease)</th>
<th>Stage 4–5 (severe disease)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulphonylureas (first generation)</td>
<td>Carbutamide</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Sulphonylureas</td>
<td>Glipizide</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>(second generation)</td>
<td>Glyburide</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
</tr>
<tr>
<td></td>
<td>Gliclazide</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>2G-GLP-1 analogues</td>
<td>Acarbose</td>
<td>Contraindicated in patients with GFR &lt; 25 mL/min</td>
<td>Contraindicated in patients with GFR &lt; 25 mL/min</td>
</tr>
<tr>
<td>GLP-1 analogues</td>
<td>Miglitol</td>
<td>No restrictions</td>
<td>No restrictions</td>
</tr>
<tr>
<td>DPP-IV inhibitors</td>
<td>Saxagliptin</td>
<td>Limited data</td>
<td>Half dose</td>
</tr>
<tr>
<td></td>
<td>Vildagliptin</td>
<td>Avoid</td>
<td>Half dose</td>
</tr>
<tr>
<td></td>
<td>Sitagliptin</td>
<td>Avoid</td>
<td>No restrictions</td>
</tr>
<tr>
<td></td>
<td>Liraglutide</td>
<td>Limited data</td>
<td>No restrictions</td>
</tr>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td>Contraindicated when GFR &lt; 60 mL/min</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Repaglinide</td>
<td>May be used with caution</td>
<td>May be used with caution</td>
</tr>
<tr>
<td>GLP-1 analogues</td>
<td>Exenatide</td>
<td>Limited data</td>
<td>Avoid</td>
</tr>
<tr>
<td></td>
<td>Liraglutide</td>
<td>Limited data</td>
<td>No data</td>
</tr>
<tr>
<td>DPP-IV inhibitors</td>
<td>Sitagliptin</td>
<td>Avoid</td>
<td>No restrictions</td>
</tr>
<tr>
<td></td>
<td>Vildagliptin</td>
<td>Avoid</td>
<td>No restrictions</td>
</tr>
<tr>
<td></td>
<td>Saxagliptin</td>
<td>Half dose</td>
<td>Half dose</td>
</tr>
<tr>
<td></td>
<td>Linagliptin</td>
<td>No restrictions</td>
<td>No restrictions</td>
</tr>
</tbody>
</table>


drugs in patients with renal insufficiency. Metformin has been implicated in cases of lactic acidosis in patients with renal failure [46], although several reviews have shown that the risk is moderate and often linked to inappropriate use of the drug or the presence of other risk factors for lactic acidosis [47–50]. Nevertheless, metformin is contraindicated in patients with renal insufficiency (creatinine clearance less than 60 mL/min), although this contraindication may differ in terms of labels for generics or when metformin is included in a fixed combination.

In addition, due to a lack of data, alpha-glucosidase inhibitors are also not recommended when creatinine clearance is less than 25 mL/min/1.73 m², and restrictions are also listed for glucagon-like peptide (GLP)-1 receptor agonists (due to limited or no data) and dipeptidyl peptidase (DPP)-IV inhibitors such as sitagliptin (creatinine clearance < 50 mL/min) and vildagliptin. Recently, half-dose saxagliptin (2.5 mg) was approved in Europe for adults with T2DM and moderate-to-severe renal impairment (although, so far, it is not reimbursed in France). Linagliptin, the latest DPP-IV inhibitor authorized in the US and EU, is the first drug of this class to have no restrictions of use in renal-impaired patients as it is mainly eliminated through bile excretion [51].

Furthermore, repaglinide, which is also mostly eliminated by the liver, may be used at full dose in patients with impaired renal function. However, it is recommended that the dosage be carefully adapted in subjects with renal impairment as the repaglinide maximum serum concentration (C_{max}) may be significantly higher in such patients compared with healthy subjects.

7.1. Management of glycaemia and progression of kidney disease in T2DM patients

In the Kumamoto (Japan) study, the development and progression of renal disease were reduced significantly in patients who received intensive treatment for their diabetes. Six years after starting treatment, only 7.7% of those treated intensively had developed microalbuminuria compared to 28% of patients treated conventionally [40]. Over the same period of time, only 11.5% of patients with microalbuminuria at inclusion had progressed towards macroalbuminuria in the intensive-treatment arm versus 32% in the conventional arm (P = 0.04). After 8 years, the incidence of microalbuminuria and progression to macroalbuminuria were 11.5% versus 43.5% and 16% versus 40% in the two study arms, respectively (P = 0.04) [44].

In the UKPDS, the risk of developing microalbuminuria in intensively treated patients after 9 years was 24% [95% CI: 9–38%; P = 0.0006] lower than in patients treated conventionally [42]. The observed benefit was similar whether sulphonylurea or insulin was used in the intensive-treatment regimen [43]. Also, the reduction in risk of progression from microalbuminuria towards macroalbuminuria was 33% (4.4% vs 6.5% in the intensive vs conventional treatment groups, respectively), although this was not statistically significant. In the VADT [45], 17% of the intensively treated T2DM patients developed microalbuminuria compared with 35% of patients treated conventionally (P = 0.05), and only 12% of patients with microalbuminuria treated intensively progressed to macroalbuminuria versus 36% in the conventional arm (P = 0.04) [42].

However, the evidence is less clear concerning the impact of tighter glycaemia control on deterioration of GFR over time. However, the UKPDS suggested that intensive treatment was associated with a 67% reduction in the doubling of creatinine after 9 years (0.71% in the intensive arm versus 1.76% in the conventional arm; P = 0.027) [42].

The results of the Action in Diabetes and Vascular Disease: Preterax and DiaMicron Modified-Release Controlled Evaluation (ADVANCE) [52] also support the benefits of good glycaemic control by demonstrating a reduction in renal complications (including aggravation of existing nephropathy or...
the development of nephropathy) in patients treated intensively compared with those treated conventionally (hazard ratio: 0.79, 95% CI: 0.66–0.93; \( P = 0.006 \)).

Thus, the current practice guidelines emphasize the necessity of maintaining good glycaemic control in patients with diabetes whatever their renal status [16]. Target values for HbA1c are identical for patients with or without renal insufficiency [53], although some authors are more cautious and argue that HbA1c goals should be defined only after taking into account the individual status of each patient [54].

The US KDOQI recommendations specify that patients with stage 3–5 renal failure are at particular risk of developing hypoglycaemia, thus making close capillary blood glucose monitoring in these patients important.

### 7.2. Problems associated with the pharmacological management of glycaemia in patients with T2DM and renal disease

Three large recent studies have demonstrated that the use of intensive treatment to achieve a strict glycaemia target of less than 6.5% may come at a price [55–57]. In the ACCORD study, a three-fold higher incidence of severe hypoglycaemia requiring medical assistance was observed with intensive treatment (10.5% vs 3.5% in the conventional therapy arm) [55]; hypoglycaemia was probably implicated in the excess mortality seen in this arm [58,59], although a recent retrospective analysis has questioned the association [60]. A nearly two-fold higher incidence of severe hypoglycaemia was also observed in the ADVANCE study (2.7% vs 1.5%) [56], whereas a five-fold higher incidence was seen in the US VADT (2% vs 10%) [57] with the use of intensive treatment regimens. In the latter study, the occurrence of severe hypoglycaemia in the last 3 months was a major predictive factor for cardiovascular mortality. Such excess mortality was particularly seen in frail patients who had suffered from diabetes for many years and who also probably had some degree of renal disease.

However, despite the problem of hypoglycaemia, the use of intensive treatments is still likely to be beneficial for cardiovascular morbidity if antidiabetic treatment is started early in patients who have not yet developed macrovascular complications. The UKPDS patients with newly diagnosed diabetes showed a significant reduction in myocardial infarction (MI) after 10 years in those initially treated intensively [61]. These results were confirmed in a review of the ACCORD, ADVANCE and VADT [62], as well as in a meta-analysis by Ray et al. [40] that showed a significant reduction in MI of 17% with intensive treatment, with no changes in overall mortality.

Preliminary data from the UKPDS also showed that the incidence of severe hypoglycaemia (requiring medical treatment) in 922 newly diagnosed T2DM patients treated with sulphonylureas was 0.7% per year [63]. In the final results, over the 10 years of the study, the average proportion of patients presenting each year with one or more episodes of severe hypoglycaemia was 0.6% in patients treated with glibenclamide, and 17.7% when all episodes of hypoglycaemia were taken into account [61]. In the study by van Staa et al. [64], the annualized risk of hypoglycaemia was 1.8% in patients treated with sulphonylureas. These data demonstrate the importance of having effective antidiabetic drugs that do not increase the risk of hypoglycaemia in T2DM, especially when patients have signs of renal disease.

### 7.3. Management of T2DM patients with renal insufficiency in France

As renal insufficiency can modify the metabolism of insulin and certain oral antidiabetics, the monitoring and adaptation of these treatments according to the evolution of renal insufficiency are recommended [52].

Analysis of the ENTRED 2007 data showed that renal insufficiency was taken into account in the choice of treatment for T2DM patients in France, and led to an increased use of insulin, particularly insulin alone, at the expense of an oral antidiabetic drug (OAD) as monotherapy for those with the most advanced stages of renal disease (3b, 4 and 5; Table 3). More recently, analysis of GP data from the Cegedim Strategic Data (CSD) Thalès network also documented a higher percentage of patients with advanced renal disease treated with insulin monotherapy (Table 3).

Examination of the prescription of antidiabetic drugs by class showed that chronic renal disease is generally, but not always, taken into account in the choice of hypoglycaemic drug (Table 4). Thus, in the ENTRED 2007 study as in the CSD Thalès network, biguanides were less often used in cases of severe renal insufficiency (stages 3b, 4 and 5; Table 4), whereas the use of glinides and insulin increased with more severe renal disease. Even more surprisingly, both data sources noted a slight increase in the use of sulphonylureas, while the proportion of patients receiving glitazones (thiazolidinediones) appeared to decrease with the stage of renal disease, even though this class of drugs was not officially contraindicated for this situation at the time of data collection. Nevertheless, it was surprising that a significant proportion of French T2DM patients with severe renal insufficiency (stage 3b or higher) were still being treated with biguanides, known to be contraindicated in renal conditions (Table 2).

### 8. Management of renal insufficiency in patients with T2DM in France

The prompt management of chronic renal insufficiency as soon as it appears can slow its progression and significantly delay dialysis or transplantation. As first-line treatments, the ANAES 2004 recommended: (i) restriction of sodium to 100 mmol/d (6 g/d) (professional agreement); and (ii) an angiotensin-II receptor antagonist (ARA2) for T2DM (grade A) [51]. In the French patients included in the ENTRED 2007 [5] and ECODIA 2005 [7] studies, there was no marked difference in the use of the different classes of drug for renal disease (ARA2s only, ACE inhibitors only, or both or none) according to the stage of renal disease. Although, in the ENTRED 2007 study, ARA2s alone appeared to be slightly less frequently used in stages 3b, 4 and 5,
Table 3
Oral antidiabetic drug (OAD) and insulin therapy in patients with type 2 diabetes in France, according to stage of chronic kidney disease (CKD).

<table>
<thead>
<tr>
<th>Patients without CKD or stage 1 with normal or increased GFR</th>
<th>Patients without CKD or stage 2 with slightly decreased GFR</th>
<th>Stage 3a (moderate CKD)</th>
<th>Stages 3b, 4, 5 (moderate, severe, end-stage CKD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ENTRED 2007 data</strong> (n = 1543)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy (%)</td>
<td>41</td>
<td>47</td>
<td>52</td>
</tr>
<tr>
<td>Bitherapy (%)</td>
<td>32</td>
<td>27</td>
<td>23</td>
</tr>
<tr>
<td>Tritherapy or more (%)</td>
<td>12</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Insulin only (%)</td>
<td>4</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Insulin + OAD (%)</td>
<td>11</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td><strong>CSD Thales data</strong> (n = 26,259)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy (%)</td>
<td>45</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Bitherapy (%)</td>
<td>31</td>
<td>29</td>
<td>28</td>
</tr>
<tr>
<td>Tritherapy or more (%)</td>
<td>13</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Insulin only (%)</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Insulin + OAD (%)</td>
<td>8</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

GFR: glomerular filtration rate; CSD: Cegedim Strategic Data.

* This is a computer-based network of 1200 general practitioners (GPs) contributing extensive anonymous data on patient consultations and treatment to a centralized electronic database for subsequent outcome follow-up. The participating GPs are representative of the French GP population according to three main criteria: geographical area; age; and gender; their activity and prescription habits were compared *a posteriori* with the national data and proved to be representative. The database currently includes records for more than 1.6 million patients routinely collected since 2002.

Table 4
Type of hypoglycaemic agents used in patients with type 2 diabetes in France, according to stage of CKD.

<table>
<thead>
<tr>
<th>Stage 1 or normal</th>
<th>Stage 2</th>
<th>Stage 3a</th>
<th>Stages 3b, 4, 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ENTRED 2007 data</strong> (n = 1543)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin (%)</td>
<td>14</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>Biguanides (%)</td>
<td>74</td>
<td>62</td>
<td>50</td>
</tr>
<tr>
<td>Sulphonylureas (%)</td>
<td>49</td>
<td>51</td>
<td>52</td>
</tr>
<tr>
<td>Glinides (%)</td>
<td>8</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors (%)</td>
<td>8</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Thiazolidinediones (%)</td>
<td>20</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td><strong>CSD Thales data</strong> (n = 26,259)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin (%)</td>
<td>9</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Biguanides (%)</td>
<td>67</td>
<td>62</td>
<td>54</td>
</tr>
<tr>
<td>Sulphonylureas (%)</td>
<td>37</td>
<td>41</td>
<td>42</td>
</tr>
<tr>
<td>Glinides (%)</td>
<td>6</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors (%)</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Thiazolidinediones (%)</td>
<td>13</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>DPP-IV inhibitors (%)</td>
<td>20</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>GLP-1 analogues (%)</td>
<td>0.6</td>
<td>0.7</td>
<td>0.5</td>
</tr>
</tbody>
</table>

CSD: Cegedim Strategic Data; DPP-IV: dipeptidyl peptidase-IV; GLP-1 glucagon-like peptide-1.

this was not observed in the ECODIA survey. Alarmingly, more than one-third of patients with renal disease in the two studies were not being treated with a kidney-protective drug whatever the stage of renal insufficiency.

9. Conclusion

Diabetes and chronic renal disease are closely linked: diabetes can lead to the development of renal disease, whereas aggravation of renal disease can, in some cases, give rise to hyperglycaemia itself. Furthermore, hyperglycaemia arising from poorly controlled diabetes can lead to deterioration of renal function, particularly in elderly patients. The continuing increases in the prevalence of diabetes and the ageing of the diabetic population make chronic renal disease an important medical–economic problem. Diabetes and chronic renal disease are both independent risk factors for cardiovascular disease, but they also act synergistically to increase cardiovascular morbidity and mortality. Cardiovascular risk may be further increased by the concomitant presence of other risk factors such as high blood pressure, dyslipidaemia, obesity and physical inactivity.

Hypoglycaemia also plays a role in cardiovascular morbidity and mortality: the cardiovascular risk in diabetes patients with renal insufficiency may be further raised by the increased risk of hypoglycaemia associated with renal insufficiency.

The optimal target levels of glycaemia in patients with different stages of renal disease remain unclear. In contemporary practice guidelines, HbA1c targets are similar to those for the general population, but these guidelines also highlight the risk...
of hypoglycaemia in T2DM and recommend the adaptation of treatment for each individual patient, with more ambitious individual HbA1c goals for older patients with chronic kidney disease.

Current recommendations for the management of T2DM patients include regular screening for nephropathy, prophylaxis with ACE inhibitors/ARA2s, tight glycaemic control and pharmaceutical management, while avoiding treatments that may further compromise renal function.

Important improvements have been achieved in France in the management and monitoring of patients with T2DM over the past few years, although screening for nephropathy still relies on the measurement of creatininemia.

Deterioration of renal function modifies the clearance of hypoglycaemic treatments and reduces renal neoglucogenesis, and may sometimes induce insulin resistance.

Intensification of antidiabetic treatment should be closely monitored and aim to decrease cardiovascular risk. It should also attempt to avoid both hyperglycaemia and hypoglycaemia, although this may be particularly difficult in patients with renal insufficiency. Some progress has been made in this area, although T2DM management often still depends on drugs that are contraindicated or need to be used with caution in patients with renal disease. For this reason, the availability of effective hypoglycaemic drugs with no significant side effects, and which are well-tolerated by the kidneys and eliminated by a route other than the kidneys, constitute a significant therapeutic advance in the treatment of diabetes. Intensified multifactorial interventions with tight glucose regulation, and the use of renin–angiotensin system blockers, aspirin and lipid-lowering agents, would also reduce the risk of non-fatal cardiovascular disease among patients with both T2DM and microalbuminuria [65].

Disclosure of interest

B. Detournay and O. Clement are consultants for CEMKA-EVAL, a company providing consultancy services for most pharmaceutical companies and public institutions involved in health care in France.

D. Simon has received consulting fees or honoraria from Astra-Zeneca, Boehringer-Ingelheim, GlaxoSmithKline, Bristol Myers Squibb, Novartis, Lilly-France, Novartis, Pfizer, Sanofi-Aventis, Servier, Takeda.

P.J. Guillausseau has received honoraria for lectures and consultations from Astra-Zeneca, Bristol-Meyer Squibb, Eli-Lilly, GlaxoSmithKline, Lifescan, Novartis, Novo-Nordisk, Roche, Sanofi-Aventis, Servier, and Takeda.

D. Joly has received honoraria from Boehringer-Ingelheim, Novartis, Amgen and Genzyme for lectures and consultancy.

B. Vergès has received, during the past three years, consulting fees and honoraria for lectures from AstraZeneca/Bristol-Myers Squibb, Bayer Pharma, Lilly, Boehringer, Merck Sharp Dohme-Chibret, Novartis Pharma Novo Nordisk, Sanofi Aventis, Servier and Takeda.

C. Attali has received honoraria from Boehringer-Ingelheim, Novartis and Bristol Meyer Squibb.

Y. Briand and O. Delaître are employed at Boehringer-Ingelheim France SAS.

References


