

Treating Elderly People with Diabetes and Stages 3 and 4 Chronic Kidney Disease

Cataldo Abaterusso,* Antonio Lupo,* Vittorio Ortalda,* Vincenzo De Biase,* Antonello Pani,[†] Michele Muggeo,[‡] and Giovanni Gambaro*

Divisions of *Nephrology and [†]Endocrinology, Department of Biomedical and Surgical Sciences, University Hospital of Verona, Verona, and [‡]Division of Nephrology, "Brotzu" Hospital, Cagliari, Italy

Dedicated European and US clinical guidelines for type 2 diabetes in the elderly have been released, but they do not specifically address the issue of advanced chronic kidney disease (CKD) in older patients with diabetes. General clinical guidelines have been published on the treatment of patients with diabetic nephropathy (DN), but these address the issue of how to prevent progression and treat advanced DN without distinguishing between different age groups. Elderly patients with diabetes and stages 3 to 4 CKD have particular needs that differ from those of younger patients with the same conditions. This is mainly due to their frailty and shorter life expectancy. Differently tailored therapeutic strategies are needed, which may have less stringent targets; and the use of common drugs should be critically evaluated. The management agenda (metabolic control, low-protein diet, controlling BP, preventing progression of advanced DN, preventing cardiovascular outcomes) for these patients is discussed in light of the limits and perspectives of current guidelines. Intensive, simultaneous management of all items on the agenda may not be feasible for a proportion of older patients, and clinicians may have to give priority to reducing some risk factors rather than others, choosing between different therapies.

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In 2004, the European Diabetes Working Party for Older People launched its "Clinical Guidelines for Type 2 Diabetes Mellitus" specifically dedicated to the elderly (the European Diabetes & Aging Guidelines for short [EDAG]) (1). Guidelines for Improving the Care of the Older Persons with Diabetes Mellitus were also developed in the United States in 2003 (American Diabetes & Aging Guidelines for short [ADAG]) (2). There is a dual rationale behind guidelines specifically dedicated to the elderly. First, older people with diabetes have special needs. Second, with the demographic changes occurring in Western populations, the number of elderly individuals with diabetes is expanding dramatically. These people's life expectancy is considerably reduced: Whereas a 74-yr-old Western man without diabetes has an average life expectancy of approximately 10 yr and a woman of approximately 12 yr, when they have diabetes, their life expectancy is roughly 4 and 6 yr shorter for men and women, respectively (3).

Demographic changes in Western populations also have a significant impact on renal care. In many Western countries, the elderly now represent the most rapidly growing population initiating dialysis. In the United States, the median age of the incident population starting renal replacement therapy reached 64.6 yr in 2005, and the incidence of ESRD by age >75 yr was

approximately 1500 pmp, 750 in Canada, and 500 in Italy (4). Because the prevalence of diabetes has been increasing among the elderly, it is hardly surprising that elderly individuals with diabetes contribute substantially to the overall burden of stage 5 chronic kidney disease (CKD) in Western countries. In 2005, in fact, one third of the incident cases of ESRD in the United States in people who were older than 75 yr had diabetic kidney disease (4).

Two very recently released publications are also of interest in the present contention, the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease (5) and the Quality Indicators for the Care of Vulnerable Elders (the Assessing Care of Vulnerable Elders 3 [ACOVE-3] initiative) (6). Only the former marginally addresses the issue that elderly people with diabetes and CKD warrant special treatment considerations, but neither of them nor the EDAG and ADAG specifically addresses the topic of advanced CKD in older patients with diabetes. This review aims to make up for this shortcoming relating to the treatment of elderly people with diabetes and advanced renal impairment (*i.e.*, in stages 3 and 4 CKD). As the lower age limit, we consider patients between 70 and 80 yr because such long-lasting patients with diabetes are most likely to have a considerably reduced life expectancy and a number of diabetes-related comorbidities. The relevant clinical issue here, however, is the patients' vulnerability, not their age, so our considerations could also be extended to younger, frail patients with diabetes and stages 3 to 4 CKD.

An attempt has been made to quote and grade the level of

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Correspondence: Prof. Giovanni Gambaro, Divisione di Nefrologia, Dipartimento di Scienze Biomediche e Chirurgiche, Università di Verona, Ospedale Maggiore, P.le Stefani 1, 37126 Verona, Italy. Phone: +39-045-8122521; Fax: +39-045-915176; E-mail giovanni.gambaro@univr.it

evidence. There is a sizable amount of good-quality research on the prevention and management of the complications of type 2 diabetes and related aspects, but most of it is not specific to elderly patients, and none of these studies concerned elderly people with advanced CKD. Most of the suggestions have consequently been classified simply as clinical practice recommendations (CPR), at the level of “opinion-based” advice, whereas a clinical practice guideline (CPG) has been proposed in just one case.

Treating Elderly Patients with Diabetes and Stages 3 to 4 CKD: Limits and Perspectives of Current Guidelines

National (5,7–9) and international (10) clinical guidelines on the treatment of patients with diabetic CKD have three major drawbacks, especially in view of the special needs of elderly patients with diabetes. First, they generally address the issue of how to prevent progression and how to treat advanced CKD without distinguishing between different age groups. Second, the main emphasis is on intensive blood glucose control and the prevention of microvascular complications, but this may not fit the bill for patients with advanced renal disease. Third, they give the same emphasis to different renal disease progression factors (metabolic and BP control, renin-angiotensin system inhibition, control of co-factors, and diet), although they have neither the same relevance nor the same affordability. This particularly applies to elderly patients with diabetes, who may have clinical (and/or social, environmental, *etc.*) situations that affect the relative weight of such factors, which warrant a different prioritization.

Although they do not address stages 3 to 4 CKD, the ADAG (2) and the EDAG (1) do consider these issues in general terms, following the assumption that treatment for elderly patients with diabetes needs to focus on particular issues and different priorities; the guidelines emphasize what can be reasonably treated and afforded in this particular age group. The ADAG also introduce the concept of the time horizon for the benefits of certain measures: It may take as long as 8 yr for glycemic control to have a positive fallout on microvascular complications or only 2 to 3 yr for the benefits of a better control of BP and lipids to become apparent (2).

Several of these elderly patients with diabetes are frail. According to the ACOVE project, a vulnerable elder is a person who is older than 65 yr and is at increased risk for death or functional decline in a 2-yr period (6). Patients with diabetes and stages 3 to 4 CKD considered in this review most likely belong to this category. This is because advanced CKD dramatically reduces life expectancy and is quite frequently associated with macrovascular clinical manifestations and neuropathy in patients with diabetes (11,12). Cardiovascular mortality and morbidity rates are extremely high in patients with diabetes and CKD (13). The EDAG emphasize that ischemic heart disease (IHD) is the most common cause of death in elderly people with type 2 diabetes, but peripheral artery disease, the strongest mortality predictor in patients with ESRD (14), and heart failure (HF) (12) are also very prevalent in these patients. It is

obvious from these considerations that the treatment agenda for elderly patients with type 2 diabetes and stages 3 to 4 CKD needs to be reconsidered, and key issues in such a reassessment will concern treatment tailoring and simplification and prioritization.

Treatment Agenda

Given the frailty and high cardiovascular risk of elderly patient with type 2 diabetes and stages 3 to 4 CKD, the issue is whether metabolic control, prevention of CKD progression, prevention of cardiovascular outcomes, BP control, and nutritional treatment should be interpreted differently in these particular patients *vis à vis* the general patients with diabetes.

Metabolic Control

The recent KDOQI document (5) emphasizes that much of the support for strict metabolic control to improve kidney outcomes in patients with diabetes arises from the favorable effect on the onset of microalbuminuria, whereas there is only weak evidence of a beneficial effect on progression to more severe stages of CKD. The EDAG also emphasize that there is no clear evidence that strict glycemic control is effective in preventing macrovascular (cardiovascular) complications in middle-aged patients with type 2 diabetes. Although several studies involving older patients demonstrated high complication and mortality rate correlating with poor blood-sugar control (15), no randomized, controlled trials have assessed the impact of optimal glucose control on primary cardiovascular disease prevention for the older patients with diabetes, whereas in younger patients, it is unsuccessful (16) (Table 1) or may even increase cardiovascular mortality (17).

It is therefore best to take a prudent approach to treating hyperglycemia in elderly patients with advanced CKD, a number of comorbidities, and a limited life expectancy (1). The EDAG state that for older patients with type 2 diabetes and single-system involvement, a target glycosylated hemoglobin range of 6.5 to 7.5% should be the aim. As previously observed, it is highly unlikely, however, that no other system is involved in patients with diabetes and advanced CKD. As in frail patients, in whom the hypoglycemic risk is high and it is of paramount importance to control symptoms and prevent metabolic decompensation, the target glycosylated hemoglobin range should be 7.5 to 8.5% according to the EDAG (1), <8.0% for the ADAG (2), and <9% according to the ACOVE initiative (18). We believe that 8 to 8.5% is a reasonable compromise for these patients (CPR, opinion), because 9%, which corresponds to a mean plasma glucose of 13.5 mmol/L (19), would expose patients to hyperosmolarity complications, including the acute decline of renal function.

Treatment with an insulin secretagogue (normally a sulfonylurea) or metformin is considered the front-line therapy for older people with type 2 diabetes. Care is needed in prescribing oral hypoglycemic agents for patients with decreased renal function, however, and some should be avoided altogether because of the risk for persistent and severe hypoglycemic episodes (chlorpropamide, glyburide/glybenclamide) or life-threatening lactic acidosis (metformin). The current practice in

Table 1. Risk reduction achieved by different therapeutic strategies in the UKPDS^a

Parameter	Strict Pressure Control (%) (37)	Strict Metabolic Control (%) (16)
Microvascular complications	37	25
Retinopathy	34	21
Diabetes-related deaths	32	10 (NS)
Stroke	44	NS
Congestive HF	56	NS
MI	21 (NS)	NS
Amputation	49 (NS)	NS

^aPercentages are statistically significant, unless otherwise specified. HF, heart failure; MI, myocardial infarction; UKPDS, UK Prospective Diabetes Study.

such cases is to switch patients from oral therapy to insulin treatment because of the hypoglycemic risk, although some national guidelines, including the French ALFEDIAM-SFN report, suggested that oral antidiabetic agents may be considered on a case-by-case basis (9), and the recent KDOQI document (5) considered the possibility of using glipizide and gliclazide without any dosage adjustment in stages 3 and 4 CKD. Oral hypoglycemic agents are currently used to treat 8% of prevalent patients with ESRD in Canada and 30% in France (19,20). Insulin treatment should also be considered with caution, however, in terms of the hypoglycemic risk, because exogenous insulin is eliminated primarily by the kidney. In French patients with diabetes, the incidence of sulfonylurea-related severe hypoglycemic episodes was 1.2% patient/yr, whereas for sulfonylurea and insulin in combination, it was 2.7%, and for insulin alone, it was 3% (20). The vast majority of these episodes are associated with old age, errors in drug dosage, drug interactions, and the initial period of treatment, whereas renal impairment is less important (20). Death, which happens in 4.9 to 12% of cases of severe hypoglycemia, occurs only in patients with severe concomitant diseases (21).

Renal impairment has not been reported as notably predisposing patients to severe hypoglycemia induced by the sulfonylurea glipizide, the clearance and half-life of which are unaffected by renal function (22). Thus, if a sulfonylurea is used for patients with stages 3 to 4 CKD, the best choice is glipizide without dosage adjustment.

Unlike nateglinide, the nonsulfonylurea insulin secretagogue repaglinide can also be used in stages 3 to 4 CKD without any dosage adjustment (5,23). No relationship was found between the degree of renal impairment (GFR as low as 20 ml/min) and the risk for hypoglycemia in patients who were treated with repaglinide (23).

Thiazolidinediones are interesting oral agents that reduce insulin resistance. Adverse effects include fluid retention, edema, and congestive HF. The consensus is to exclude patients with New York Heart Association class 3 and 4 HF from this treatment. Two recent meta-analyses (24,25) suggested that rosiglitazone is associated with a significant increase in the risk for myocardial infarction (MI) and HF. A third meta-analysis on patients who were treated with pioglitazone reached partly different conclusions, because its use was associated with a

significantly lower risk for death, MI, or stroke among patients with diabetes, but the risk for severe HF increased (26). Because both rosiglitazone and pioglitazone are almost entirely metabolized by the liver and the major metabolites do not accumulate in patients with stages 3 to 4 CKD, no dosage adjustment is necessary. Although pioglitazone was safe and well tolerated in a small group of patients with varying degrees of CKD (27), and according to a *post hoc* analysis of the PROactive trial patients who had diabetes and GFR <60 ml/min and were treated with pioglitazone were less likely to develop major cardiovascular events (28), and finally combined therapy with rosiglitazone and sulfonylureas was well tolerated in 301 patients with diabetes and GFR 30 to 80 ml/min (29), we believe that for the time being, the results of the three meta-analyses advise against their generalized use in patients with such high cardiovascular risk as those discussed here (CPR, opinion). As for acarbose, because experience is lacking on its long-term use in patients with advanced CKD, its generalized use is not recommended for the time being (5,20) (CPR, opinion) although no major adverse effect has been reported.

With regard to insulin, it is eliminated primarily by the kidney. The pharmacokinetics of various insulin preparations have not been studied sufficiently in patients with varying degrees of renal dysfunction, but the new long- and short-acting insulin analogs do not seem to have any better pharmacokinetics in patients with CKD. To reduce the risk for hypoglycemic episodes, insulin dosage reduction of 25% has been recommended in renal patients with GFR 10 to 50 ml/min, but, when the long-acting insulins glargine or detemir are used, it may be wise to start treatment with 50% of the usual initial dosage of 0.1 U/kg, titrating the dosage until target fasting glucose concentrations are reached. In “treat-to-target” studies, the addition of a basal insulin (glargine) to regimens with oral medication significantly improved metabolic control, resembling the effect of neutral protamine Hagedorn insulin, while reducing the number of nocturnal hypoglycemic episodes (30).

In our opinion, when oral treatment with glipizide, gliclazide, or repaglinide is not sufficient, the use of acarbose and, in selected cases, of pioglitazone should be considered to minimize the emotional burden associated with insulin therapy. If, notwithstanding the less stringent targets for metabolic control in these patients, oral treatment alone is not adequate, then the

combination with the insulin analog glargine in the evening might be considered as the front-line treatment for elderly patients with diabetes and stages 3 to 4 CKD, rather than multiple insulin injections, given the need to simplify the treatment as much as possible (CPR, opinion).

Preventing Advanced CKD Progression to ESRD versus Preventing Cardiovascular Outcomes

Individually, both diabetes and CKD are cardiovascular risk factors, but together they synergistically increase cardiovascular mortality (13), so patients with type 2 diabetes and nephropathy are more likely to die than to progress to more severe CKD stages (11). What is peculiar to elderly patients with diabetes and CKD by comparison with younger patients with same clinical conditions is the time horizon, which may leave little scope for a worthwhile prevention of CKD progression, although there may be time enough for the cardiovascular prevention.

The EDAG suggest tailoring a multitarget approach to elderly patients with diabetes according to the severity of cardiovascular risk, but there is no doubt that elderly patients with diabetes and CKD belong to the very high-risk group (11,12). Very few trials, if any, have investigated the effect of the usual treatments for containing cardiovascular risks in elderly people or patients with CKD, and medications that are used in the general population for cardiovascular event prevention are underprescribed in patients with CKD, especially when they are elderly (31) and have diabetes (32), although observational studies suggested that elderly patients with stages 3 to 4 CKD or diabetes benefit from such standard treatments at least as much as patients with a preserved renal function. Furthermore, cumulative incidence curves from lipid- and BP-lowering trials indicated that cardiovascular benefits start after 2 to 4 yr of treatment, which makes these treatments worthwhile even for patients with a short life expectancy (33). These observations show that a multifaceted approach to cardiovascular risk factors is even more essential to optimize cardiovascular outcomes in elderly patients with diabetes and CKD than in other age groups (CPR, moderate).

BP Control

Controlling hypertension may, in theory, be worthwhile to contain both the progression of nephropathy and the cardiovascular risk in the patients with whom we are dealing. Judging from the KDOQI analysis (5), however, most of the evidence (classified as weak) supporting a favorable effect of BP control on CKD progression in patients with diabetes is supported by trials of patients with stages 1 to 2 CKD. Only angiotensin II receptor blockers (ARB) have been tested on patients with type 2 diabetes and more severe CKD, including stage 3, and shown to reduce GFR decline, but this seems to be partially independent of BP changes and due to a specific nephroprotective effect (34,35). Conversely, according to a meta-analysis of approximately 1900 patients who had diabetes (most of them with stages 1 and 2 CKD) and were treated with angiotensin-converting enzyme inhibitors (ACEI), the evidence that ACEI reduce the risk for stages 3 to 5 CKD is weak (36).

As regards elderly patients with diabetes in particular, unfortunately no evidence-based medical conclusions (EBM) can be drawn on the progression of renal disease from the available clinical trials. Because of its long follow-up, only the UK Prospective Diabetes Study (UKPDS) helps to some degree. The most significant results were obtained on cardiovascular complications rather than on microangiopathies, and strict BP control proved better for their prevention than strict metabolic control (16,37) (Table 1). Thus, in patients with type 2 diabetes and stages 3 to 4 CKD, the available evidence in favor of controlling hypertension seems to be particularly important to the prevention of cardiovascular risks.

The benefits of a lower BP on the cardiovascular risk in the very old is confirmed by a meta-analysis on trials conducted on antihypertensive agents in the subgroup of patients who were older than 80 yr, which concluded that treatment reduces the risk for strokes, major cardiovascular events, and HF by 34, 22, and 39%, respectively (38), hence the EDAG statement that in patients who are older than 75 yr and have type 2 diabetes BP control should never take second place *vis à vis* other therapeutic options (*e.g.*, blood glucose control). We believe that this should be extended to elderly patients with diabetes and advanced CKD (CPR, opinion).

Both the ADAG and the EDAG suggest that the threshold for treating high BP in older people with type 2 diabetes should be 140/80 mmHg. This is based on the likelihood of reducing the cardiovascular risk in older individuals balanced against issues relating to tolerability, clinical factors and disease severity, and targets that are likely to be achievable. According to the EDAG, a lower BP should be aimed for in cases with concomitant CKD, but for vulnerable patients, when HF and stroke prevention is more important than slowing the progression of microvascular complications, BP <150/90 mmHg are proposed as acceptable; however, the recent ACOVE-3 guidelines suggested for vulnerable elderly patients different systolic targets according to different clinical conditions but anyway <140 mmHg (39). Thus, although most elderly patients with diabetes and stages 3 to 4 CKD likely belong to the category of frail patients, a goal of 140/90 seems to be reasonable with exceptions depending on tolerability and the patient's safety (CPR, opinion).

As for the choice of antihypertensive drugs for elderly patients with diabetes and nephropathy, the EDAG recommend ACEI. The use of short-acting calcium channel blockers and α -adrenoreceptor blockers is discouraged. The ADAG do not take a stand on the priority of certain classes of antihypertensive agents, whereas they do highlight that, according to EBM (36), diuretics, ACEI, β blockers, and calcium antagonists have comparable effectiveness in reducing cardiovascular morbidity and mortality. The ACOVE-3 discourages the use of first- or second-generation calcium antagonists (verapamil, diltiazem, and nifedipine) in patients with HF because of safety concerns (40).

Elderly patients with diabetes and stages 3 to 4 CKD are likely to need more than one agent to achieve the target BP, however. We suggest that diuretics be considered whenever possible (CPG, strong). The long-term results of the Systolic Hypertension in Europe (SHEP) trial are quite impressive (41);

even a modest dosage of a mild diuretic was sufficient to reduce cardiovascular and all-cause mortality, particularly in patients with diabetes. When it comes to choosing additional agents, we should also consider β blockers for those with HF or IHD (see the section on β -blockers on the next page).

The EDAG do not rely on the EBM emerging from the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study (34) or the Irbesartan Diabetic Nephropathy Trial (IDNT) (35), because they recommended ACEI (consensus-based statement) for elderly patients with type 2 diabetes and nephropathy and ARB only when the former are not tolerated or are contraindicated. The ACOVE-3 suggested instead that either ACEI or ARB be used in patients with diabetes and CKD, especially when they have a history of heart disease. ARB have proved capable of slowing the progression of advanced CKD in patients with type 2 diabetes (34,35), although they were not powered to demonstrate an effect on cardiovascular end points. After the publication of some challenging meta-analyses, there is much debate on the superiority of ACEI over ARB in terms of preventing cardiovascular mortality (42), and even a rough comparison of the effect of different agents on cardiovascular risk in the subgroup of elderly patients with type 2 diabetes from several controlled trials on hypertension showed that lowering BP reduced the cardiovascular risk whatever drug was being used, but ARB were not the most effective (Table 2). We therefore agree with the EDAG statement that, in patients such as those discussed here, for whom preventing cardiovascular outcomes is more important than delaying progression to ESRD, ACEI should be first-line therapy and ARB should be the next best choice when the former cannot be used.

The use of ACEI (or ARB) in elderly patients with diabetes and nephropathy should be watchful, however, because agents

that affect the renin-angiotensin system may have serious adverse effects (*e.g.*, an acute decrease in renal function, hyperkalemia, acceleration of progression to ESRD), particularly in these patients (43,44). They should not be seen as the panacea for treating patients with diabetes and nephropathy. In the Third National Health and Nutrition Examination Survey (NHANES III), 34% of the patients who had nonmicroalbuminuria and type 2 diabetes and were aged 60 to 79 yr had a GFR <30 ml/min, and 47% were between 30 and 60 ml/min (45). These nonproteinuric renal conditions progress quite differently (*i.e.*, very slowly) by comparison with typical DN and CKD, as shown by data from the Heart Outcomes Prevention Evaluation (HOPE) and the RENAAL trials (46,47) suggesting a CKD that differs from diabetic glomerulopathy (atherosclerosis related?) and may not benefit from the same favorable effect of ACEI and ARB in terms of progression to ESRD.

Controlling Cholesterol Levels

High blood lipid levels are a known independent cardiovascular risk factor. Previous statin trials indicate that an absolute reduction in LDL cholesterol produces proportionally comparable cardiovascular risk reductions in older and younger people, with or without CKD. Benefits may become apparent quite early. In the Heart Protection Study, which included patients who had diabetes and were between 40 and 80 yr and were treated with simvastatin 40 mg/d, a reduction in the risk for MI and stroke was observed within <12 mo, regardless of age or serum creatinine levels (48). Although they did not analyze the effect of age, two meta-analyses of pravastatin trials showed that the treatment was equally effective on mortality and cardiovascular end points in patients with and without CKD (at least up to stage 3 CKD), with and without diabetes (49,50). According to the KDOQI document (5), all patients with dia-

Table 2. Randomized, controlled trials on antihypertensive agents in elderly patients^a

Trial	Year	Age (yr)	CV Risk Reduction in Patients with Type 2 Diabetes	Experimental Drug
HOT (52)	1998	Mean 61.5	Major cardiovascular events 51% (target diastolic <80 mmHg)	Felodipine
Syst-EUR (65)	1998	>60	All cardiovascular events 69%	Nitrendipine
MICRO-HOPE (66)	2000	Mean 65	MI 22%; stroke 37%	Ramipril
LIFE (67)	2000	Mean 67	Major cardiovascular events 24%	Losartan
RENAAL (34)	2001	Mean 60	NS	Losartan
IDNT (35)	2001	Mean 58	NS	Irbesartan
CAPP (68)	2001	<66	Fatal/nonfatal MI, stroke, or cardiovascular deaths 41%	Captopril
SCOPE (69)	2005	70 to 89	NS	Candesartan
SHEP (41)	2005	>60	Cardiovascular mortality 31%	Chlortalidone

^aThe table shows only trials that were conducted on patients with diabetes or in which separate data were available for patients with diabetes. Some of the trials (33,34) were not statistically powered to demonstrate an effect on CV mortality. CAPP, Captopril Prevention Project; HOT, Hypertension Optimal Treatment; IDNT, Irbesartan Diabetic Nephropathy Trial; LIFE, Losartan Intervention For Endpoint reduction in hypertension; MICRO-HOPE, Microalbuminuria Cardiovascular Renal Outcomes (MICRO-HOPE) substudy of the Heart Outcomes Prevention Evaluation (HOPE); RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; SCOPE, Study on Cognition and Prognosis in the Elderly; SHEP, Systolic Hypertension in Elderly Program; Syst-EUR, Systolic Hypertension in Europe.

betes and stages 1 through 4 CKD should be treated, although there is no evidence to support treating stage 4 CKD, and the ACOVE-3 firmly recommended dyslipidemia treatment in all frail patients with diabetes (CPR, opinion).

Aspirin

In a systematic review of secondary prevention trials, the Antithrombotic Trialists' Collaboration (51) determined the effects of antiplatelet therapy on cardiovascular death, MI, and stroke in various categories of patients: Taking all high-risk categories together, aspirin therapy reduced nonfatal MI, nonfatal stroke, and vascular death by approximately one third, irrespective of middle or old age or diabetic condition; the effect was much the same at dosages ranging from 75 to 325 mg/d. According to the Hypertension Optimal Treatment (HOT) trial, patients who have diabetes and were aged 50 to 80 yr may benefit, in terms of major cardiovascular events, even more than patients without diabetes from treatment with aspirin 75 mg/d (52). The EDAG, ADAG, and ACOVE-3 thus suggested that older adults who have type 2 diabetes and are not on anticoagulant therapy and have no contraindications should be offered low-dosage aspirin. This should be the rule for renal patients, too, although there is no EBM for elderly patients with diabetes and renal insufficiency (CPR, opinion). Nephrologists often tend to avoid the use of aspirin because they are worried about the risk for bleeding in patients with advanced CKD, given their uremic platelet dysfunction. One of the major causes of this dysfunction is anemia, because erythrocytes play a significant part in tracking platelets to the endothelium. Nowadays, anemia is no longer a problem in renal patients, so the uremic thrombopathy issue seems to have become less important. A number of observations confirm that bleeding complications are no longer a significant problem of antiaggregation in renal patients. A Spanish group (53) showed that aspirin treatment coincided with a three-fold risk for bleeding in patients who were on hemodialysis (*versus* a two-fold risk in the general population), but optimal anemia correction was associated with reduced risk for hemorrhage. Furthermore, the US Renal Data System Dialysis Morbidity and Mortality Studies paper on the follow-up of >30,000 patient-years in patients with ESRD reported that gastrointestinal bleeding was not associated with aspirin use (54). Moreover, according to the Antithrombotic Trialists' Collaboration meta-analysis (51), patients who were on hemodialysis and were treated with low-dosage aspirin showed a statistically significant 41% reduction in major cardiovascular end points with only 2% of cases of major extracranial bleeding (very similar to the 2.3% in the general population).

β -Blockers

Large, controlled trials have shown that β blockers are highly effective in reducing the risk for cardiovascular events and death in patients who have diabetes and have sustained an MI (55). The UKPDS study on patients with type 2 diabetes and hypertension showed that β blockade was at least as effective as ACE inhibition in preventing all primary macrovascular end points (37). The use of β blockers in patients with diabetes has

generally been restricted because they are believed to impair hypoglycemia counterregulatory mechanisms; available evidence suggests, however, that β blockers are not associated with any increase in the hypoglycemic risk (19,37,56).

According to the ACOVE-3, in vulnerable elderly patients with HF or IHD, selective β blockers, such as carvedilol, metoprolol, and bisoprolol, should be offered unless the patient has a documented contraindication. Peripheral artery disease may be a contraindication to the use of β blockers, but their use is nonetheless recommended in patients with concomitant coronary heart disease (57). We therefore suggest that elderly patients with diabetes and stages 3 to 4 CKD receive β blockers unless they are contraindicated (CPR, opinion). The dosage of β blockers needs to be adapted to GFR.

Controlling Anemia

Anemia in patients with stages 3 to 4 CKD is associated with left ventricular hypertrophy, cognitive impairment, and increased general hospitalization and mortality (58). Early, appropriate anemia treatment with erythropoietin and high hemoglobin targets (13 to 15 g/dl) were thus proposed to prevent cardiovascular and noncardiovascular morbidity and mortality in patients with diabetes and CKD (58,59); however, a meta-analysis of 5143 patients also disclosed a significantly higher risk for all-cause mortality (20% more) in the higher (>13.5) than in the lower hemoglobin (<11.5) target group (60). In fact, after reviewing the latest results from randomized, controlled trials, the US National Kidney Foundation recently revised the 2006 KDOQI guidelines (61) and released (62) an opinion-based statement that hemoglobin targets should generally be in the range of 11.0 to 12.0 g/dl, independent of age and diabetes status.

Cautious Use of Potentially Nephrotoxic Agents or Procedures

Frail patients have very vulnerable kidneys, and renal function may suddenly deteriorate after various medical treatments and maneuvers. For instance, a body of evidence shows that elderly patients with diabetes may benefit like the rest of the population from a full range of cardiovascular treatments (including surgery and minimally invasive techniques), but they are at greater risk for a decline in renal function after the use of contrast agents. Adequate patient preparation before administration of contrast agents and the use of limited quantities of contrast agent may reduce this risk. A watchful use or even the temporary suspension of ACEI and ARB in conditions that favor dehydration or with the concomitant use of nonsteroidal anti-inflammatory drugs is also very important to prevent acute renal decompensation (63) and/or life-threatening hyperkalemia. Finally, any use of antialdosterone agents and nonsteroidal anti-inflammatory drugs must be very prudent, because of the risk for hyperkalemia.

Low-Protein Diet?

Low-protein diet may delay the progression of diabetic CKD, but this is not the priority of treatment in elderly patients with diabetes, and its effect is too modest and takes too long to come

Table 3. Standards of care proposed for elderly patients with diabetes and stages 3 to 4 CKD^a

Parameter	Proposed
Glycosylated hemoglobin	<8.5%
BP	<140/90 mmHg
Hemoglobin	11.0 to 12.0 g/dl
Use of a diuretic	
Use of a β blocker (carvedilol, bisoprolol, and metoprolol)	(Unless contraindicated)
Use of low-dosage aspirin or antiaggregants	(Unless contraindicated)
Use of an ACEI	(Unless contraindicated)
Use of a statin	(Unless contraindicated)
Avoidance of calcium channel blockers verapamil, diltiazem, and nifedipine	

^aACEI, angiotensin-converting enzyme inhibitor; CKD, chronic kidney disease.

about, going beyond the patient's time horizon. Even the general guidelines for patients with diabetic CKD do not recommend any restriction in protein intake (8) or advocate only a moderate reduction (0.7 to 0.9 g/kg body wt per d) provided that the caloric intake is adequate (5,7). It is also worth bearing in mind that elderly people commonly reduce their protein intake spontaneously, so it seems unreasonable to recommend any protein restriction to elderly patients with diabetes and CKD (CPR, opinion).

Conclusions

We have described the theoretical boundaries for a rational approach to the elderly patient with diabetes and advanced CKD. It is somewhere within these boundaries that a wise approach should be chosen. As a population, elderly patients with diabetes are clinically and functionally too heterogeneous to lend themselves to standardized rules (Table 3). The suggested treatment, however tailored and prioritized, for these patients is bound to be highly complex and implies polypharmacy. For some patients, an aggressive management of all of the previously discussed issues could result in harmful adverse effects (*e.g.*, episodes of hypoglycemia or of hypotension); treatments in themselves may also have a severe impact on the quality of life of elderly people and their caregivers, so it makes sense to discuss with patients what they are willing to do and what they expect to gain. Older adults do not always prefer care that prolongs their life, particularly when it is at the expense of their comfort (6). They tend to prefer to remain independent in their normal activities of daily living, to continue in their daily self-care tasks, and to avoid becoming a burden on their families (64). Depression, dementia, and functional impairment should be looked out for and considered in tailoring the treatment of these patients, contemplating any "proportionate" care and informed consent issues (6).

The strong emphasis that we have placed on the prevention and treatment of diabetic cardiovascular morbidity and mortality rather than on the secondary prevention of diabetic kidney disease in older patients with type 2 diabetes does not mean that nephrologists can do nothing for these patients—quite the reverse. The role of the nephrologist is essential in the care of these demanding patients, and at least four areas of

nephrologic pertinence can be identified. First, there are diagnostic issues to solve in patients with or without proteinuria, because not all of these renal disorders are diabetic in origin, and specific treatments may be possible or necessary. Second, there are therapeutic issues in these patients for which the nephrologist is far more experienced than any other doctor (*e.g.*, the treatment of secondary hyperparathyroidism and hyperphosphatemia, anemia, or hyperkalemia). Third, other specific problems might crop up during these patients' follow-up that are better addressed by the nephrologist (*e.g.*, a second overlapping renal disease, urinary tract infections). Fourth but very important, these patients need to be prepared for a possible switch to dialysis. Because older people with diabetes and renal failure have special needs, care must be integrated in a multidisciplinary approach.

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Disclosures

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