REVIEW ARTICLE

Inpatient Treatment of Type 2 Diabetes

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SUMMARY

Background: Type 2 diabetes is common in hospitalized patients and is often accompanied by comorbidities; it is thus reasonable to ask whether the current standard treatments for type 2 diabetes are suitable for in-hospital use. We discuss the current glucose-lowering strategies and glycemic targets and derive practical recommendations for their application in hospitalized patients.

Methods: The pertinent literature, including clinical trials, review articles, guidelines, and manufacturers' information is selectively reviewed.

Results: In critically ill patients with diabetes, the glucose concentration target value should be 140 to 180 mg/dL. In stable patients, the target should be less than 140 mg/dL in the fasting state and less than 180 mg/dL after meals. Hypoglycemic episodes should be strictly avoided. Temporary treatment with insulin is indicated for most hospitalized patients with diabetes, although oral antidiabetic agents may be continued if the hospitalization is expected to be brief. Intravenous insulin is advisable in certain situations, e.g., long operations or metabolic decompensation. Glucose-lowering strategies must be chosen individually for each patient, with consideration of the relevant comorbidities (e.g. coronary heart disease, congestive heart failure, cirrhosis, renal failure) and special conditions (e.g. prolonged fasting, administration of contrast agents, high-dose glucocorticoid treatment).

Conclusion: The treatment of patients with type 2 diabetes in the hospital is very different from their treatment at home. The particular conditions and comorbidities that can arise in the hospital necessitate flexible, individualized strategies for lowering blood glucose concentration.

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The prevalence of diabetes mellitus in Germany is 9.3% in women and 8.2% in men, according to the latest health statistics of the Robert Koch Institute (RKI) (1). Diabetes is more common in hospitalized patients than in the general population, with a prevalence of about 30% (2). The treatment of diabetes mellitus in the hospital is thus an everyday issue. The existing guidelines of the medical specialty societies cannot be directly implemented in the hospital, as they primarily concern the long-term treatment of patients with diabetes in early stages and without any major accompanying illnesses (3, 4). Most hospitalized patients with diabetes are in advanced stages of the disease, and many have accompanying illnesses and sequelae of diabetes that must be taken into account in therapeutic decision-making (5). A further difficulty arises from the ever shorter times that patients spend in the hospital (in 2009, the mean length of stay was only 8.0 days) (5). Long-term pharmacotherapy is practically impossible during such a short period of hospitalization, to say nothing of treatment based on changes of lifestyle.

The major goals of treatment during a patient's stay in the hospital include

- the safe regulation of the blood glucose concentration with moderate target values,
- the strict avoidance of hypoglycemia, and
- the initiation of long-term antidiabetic treatment or the optimization of existing treatment.

The aim of this article is to provide an overview of the purpose and scope of medical treatment options for diabetes in multimorbid hospitalized patients in the light of published guidelines from Germany and abroad, Cochrane reviews, a selective Medline search, and manufacturer-provided information on individual antidiabetic drugs.

The evidence for each of the main statements of this article will be rated with the GRADE system for evaluating evidence and recommendations in guidelines (GRADE, Grades of Recommendation, Development and Evaluation). In this system, the evidence for desired and undesired effects of treatment is designated as being of high, intermediate, low, or very low quality, while recommendations are designated as either strong or weak (6). The evidence ratings for the main recommendations given here are shown in *Table 1*.

TABLE 1

Main recommendations for the treatment of diabetes mellitus in hospitalized patients, with evidence grades

Recommendation	Evidence grade	References
The glycemic target range for acutely ill patients (e.g., in the intensive care unit) should be 140–180 mg/dL.	[2A]	(3)
For clinically stable patients on regular hospital wards, the appropriate glycemic target values are <140 mg/dL in the fasting state and <180 mg/dL postprandially.	[4B]	(3)
Temporary insulin treatment is generally recommended for hospitalized patients. If the hospital stay is expected to be short and there is no evidence of a metabolic derangement, patients can keep taking their oral antidiabetic medication as they did at home.	[4B]	(3, 8) (e4, e5)
Metformin should be temporarily discontinued at least 24 hours (preferably, 48 hours) before any planned procedures or the administration of iodinated contrast media.	[4B]	(4)
Emergency surgery is not contraindicated in patients who are currently taking metformin.	[4B]	(e6)
For patients with coronary heart disease, the goal of glycemic therapy should be a moderate lowering of the blood sugar concentration with strict avoidance of hypoglycemia.	[2A]	(10, 11) (e10–e12)
The current state of the data does not support a general recommendation for the intravenous administration of insulin, glucose, and potassium in the intensive care of diabetic patients with an acute coronary syndrome.	[2A]	(e19, e20)
Metformin is contraindicated in diabetic patients with advanced congestive heart failure (NYHA stage 3 or 4). Pioglitazone generally should not be given to patients with congestive heart failure.	[4B]	(7) (e23)
There are restrictions on the use of most oral antidiabetic drugs by patients with impaired renal function.	[4B]	(4, 7)
In hospitalized patients, base-bolus therapy yields better glycemic control than simple sliding scales.	[3A]	(20)

Evidence levels/grades of recommendation according to the GRADE scheme: the quality of the evidence is rated as high [1], intermediate [2], low [3], or very low [4], and recommendations are rated as either strong [A] or weak [B]. These evidence grades have been assigned exclusively by the authors' personal judgment. NYHA, New York Heart Association.

Glycemic targets

The German Diabetes Association (*Deutsche Diabetesgesellschaft*, DDG) recommends an HbA_{1c} value less than or equal to 6.5% as a long-term target in the outpatient treatment of type 2 diabetes. This target should be reached in three to six months. The importance of avoiding hypoglycemic episodes is explicitly mentioned; weight gain should also be avoided. An HbA_{1c} value up to 7% is acceptable if lower values can only be attained at the risk of side effects (4). The long latency of the HbA_{1c} value disqualifies it from use for blood-sugar monitoring in inpatients.

Intensified insulin regimens for glycemic control with near-normal target values have been tested for use on hospitalized patients in various situations. A basic distinction should be drawn between acutely ill patients in intensive care units and clinically stable patients on regular hospital wards.

Early trials on critically ill patients on a surgical intensive care unit (ICU) suggested a significant survival advantage for intensified insulin therapy with blood glucose targets of 80–110 mg/dL, rather than standard therapy with targets of 180–200 mg/dL (e1). These findings, however, could not be replicated in later, more extensive trials (e2, e3). A current consensus paper of the American Diabetes Association (ADA) therefore recommends that, in critically ill patients, insulin therapy should be initiated if the blood glucose concen-

tration exceeds 180 mg/dL, with a target value of 140 to 180 mg/dL (3). The recommended target values for clinically stable patients are below 140 mg/dL preprandially and below 180 mg/dL postprandially (3). Lower targets can also be aimed at in individual patients, if the risk of hypoglycemia is considered to be low (3).

Pharmacotherapy

Although the ADA recommends transient insulin treatment for most hospitalized patients (3), It would nonetheless appear reasonable to continue the patient's home regimen in the hospital if the hospital stay is expected to be short and without any metabolic derangement (e4, e5). The main oral antidiabetic drugs and their dosages and routes of elimination are listed in *Table 2*.

A number of situations will now be discussed in which the antidiabetic regimen must be adjusted during hospitalization.

Fasting periods

After a period of fasting ("nil per os," NPO), oral antidiabetic drugs should be resumed only when the patient eats the first normal-sized meal. Special recommendations are in effect for metformin and sulfonylureas. Metformin, according to the manufacturer's instructions, should be stopped 48 hours before the intended procedure and resumed only when the patient is

TABLE 2

Available drugs for the treatment of type 2 diabetes (as of 10 January 2012) (7)

Substance class	Drug	Recommended daily dose (mg/d)	Pharmacokinetics (elimination)
Biguanide	Metformin	500–2000	renal elimination by glomerular filtration and tubular secretion; elimination half-life ($t_{1/2}$) ~ 6.5 hr
Sulfonylurea	Glimepiride	1–6	after hydroxylation and carboxylation, 58% renal elimination and 35 % biliary elimination; serum $t_{1/2}$ ~ 5–8 hr
Sulfonylurea	Glibenclamide	1.75–10.5	after metabolism in the liver, 50% renal elimination and 50% biliary elimination; serum $t_{1/2}$ ~ 2–10 hr
Sulfonylurea	Gliquidone	15–120	demethylation and hydroxylation in the liver; elimination 95% biliary and 5% renal; elimination $t_{1/2}$ ~ 3 hr
Sulfonylurea	Gliclazide	30–120	metabolism in the liver, mainly renal elimination; ca. 1% unaltered metabolites in urine; elimination $t_{1/2}$ ~ 12–20 hr
Glinide	Repaglinide	1.5–16	nearly completely metabolized; elimination 92% biliary and 8% renal; elimination $t_{1/2}$: no data
Glinide	Nateglinide	120–540	metabolized mainly by hydroxylation; elimination 83% renal and 10% in stool; elimination $t_{1/2}$ ~ 1.5 hr
Glitazone (TZDs)	Pioglitazone	15–45	metabolized by hydroxylation; elimination 45% renal and 55% in stool; serum $t_{1/2}$ ~ 5–6 hr
DPP-4 inhibitor	Saxagliptin	2.5–5	still active at about 50% potency after metabolism in the liver; elimination 75% renal and 22% biliary; plasma $t_{1/2}$ ~ 2–3 hr
DPP-4 inhibitor	Sitagliptin	25–100	mainly (79%) unaltered elimination in urine; relatively little biliary elimination (13%); plasma $t_{1/2}$ ~ 12 hr
DPP-4 inhibitor	Vildagliptin	50–100	metabolized by hydrolysis, mainly in the kidneys; elimination 85% renal, 15% in stool; elimination $t_{1/2}$ ~ 2–3 hr
GLP-1 agonist	Exenatide	5 µg–10 µg	elimination by glomerular filtration and proteolysis; elimination $t_{1/2}$ ~ 2 hr
GLP-1 agonist	Liraglutid	0.6–1.8	metabolized into large proteins; no particular organ as main route of elimination; elimination of small amounts of metabolites in urine and bile; elimination $t_{1/2}$ ~ 13 hr
Alpha-glucosidase inhibitors	Acarbose	50–300	elimination >96% in stool, 1.7% renal; elimination $t_{1/2}$ ~ 9 hr
Alpha-glucosidase inhibitors	Miglitol	50–300	after resorption, eliminated in unaltered form, almost exclusively renally; elimination $t_{1/2}$ ~ 2–3 hr
Insulin	various preparations	Dose in IU	metabolized through the activity of insulin protease and insulin-degrading enzymes; inactive metabolites; elimination $t_{1/2}$ depends on insulin preparation and on resorption

TZD, thiazolidinedione; DPP, dipetidyl peptidase; GLP, glucagon-like peptide; IU, international units

reliably tolerating oral food intake, as long as there are no other contraindications (4, 7). When a patient who has been taking metformin requires emergency surgery, the metabolic situation must be monitored more closely than usual in the perioperative period (e6). If periods of fasting are already envisioned at the beginning of the patient's hospital stay, temporarily stopping treatment with sulfonylureas (SU) is recommended because of the increased risk of hypoglycemia (8). As some SUs have a longer-lasting effect (up to 72 hours), the blood glucose concentration should be checked frequently. When oral antidiabetic agents are temporarily discontinued, insulin can be given: the blood glucose concentration can be controlled either with subcutaneous insulin injections or with intravenous insulin through a perfusor pump, depending on the length and invasiveness of the procedure (8). Hourly blood glucose deter-

minations are recommended when a perfusor is used. The simultaneous infusion of a solution containing glucose seems reasonable, in order to assure adequate delivery of nutritional substrate to the cells (8). Detailed recommendations on the use of intravenous insulin infusion regimens are summarized in *Table 3* and in references (8) and (9).

Radiological contrast studies

As the use of iodinated radiological contrast media can temporarily lower the glomerular filtration rate, potentially inducing renal failure, metformin should be discontinued at least 24 hours before the radiological study and restarted no sooner than 48 hours afterward, and only if laboratory tests confirm normal renal function. Emergency studies can be performed even if the patient has been taking metformin (e7). It would also

TABLE 3

Insulin therapy recommendations for inpatients with type 2 diabetes in special clinical situations; modified from references (8, 24)

Clinical situation	Insulin therapy		Further options for glycemic control	Comments
	Basal requirement	Prandial requirement		
Regular meals	<ul style="list-style-type: none"> – NPH insulin twice daily or only in the evening – long-acting insulin analogues in the morning or evening 	<ul style="list-style-type: none"> – normal insulin or short-acting insulin analogues before meals 	<ul style="list-style-type: none"> – normal insulin or short-acting insulin analogues on a sliding scale 	<ul style="list-style-type: none"> – calculated daily insulin requirement: 0.6 IU/kgBW per day – basal insulin fraction 40–50% – avoid evening correction to prevent nocturnal hypoglycemia – administration of mixed insulins before morning and evening meals
Brief fasting period (short operations, endoscopy, catheter studies)	depending on the pre-interventional insulin dose: <ul style="list-style-type: none"> – 1/2 to 2/3 of the morning NPH insulin dose – long-acting insulin analogues in unaltered dose 	from the resumption of oral food intake: <ul style="list-style-type: none"> – continuation of preinterventional dose of normal insulin or short-acting insulin analogues 	until the resumption of oral food intake: <ul style="list-style-type: none"> – normal insulin every 4–6 hr – short-acting insulin analogues every 4 hr 	<ul style="list-style-type: none"> – unaltered pre-interventional insulin dose on the evening before the procedure – performance of the procedure as early in the day as possible
Longer fasting period (major surgery)	<ul style="list-style-type: none"> – insulin perfusor – normal insulin every 4–6 hr – short-acting insulin analogues every 4 hr depending on the pre-interventional insulin dose: <ul style="list-style-type: none"> – 1/2 of the morning NPH insulin dose – long-acting insulin analogues in unaltered dose 	–	until the resumption of oral food intake: <ul style="list-style-type: none"> – normal insulin every 4–6 hr – short-acting insulin analogues every 4 hr 	<ul style="list-style-type: none"> – use of an insulin perfusor for longer procedures – calculated starting dose when an insulin perfusor is used: 0.2 IU/kgBW per hour
Prolonged fasting period (regular hospital ward)	<ul style="list-style-type: none"> – NPH insulin twice daily or only in the evening – long-acting insulin analogues in the morning or evening 	–	<ul style="list-style-type: none"> – normal insulin every 4–6 hr – short-acting insulin analogues every 4 hr 	–
Prolonged fasting period (intensive care unit)	<ul style="list-style-type: none"> – insulin perfusor – normal insulin every 4–6 hr – short-acting insulin analogues every 4 hr 	–	<ul style="list-style-type: none"> – normal insulin every 4–6 hr – short-acting insulin analogues every 4 hr 	<ul style="list-style-type: none"> – calculated starting dose when an insulin perfusor is used: 0.2 IU/kgBW per hour – adjustment of infusion rate e.g. by the Yale protocol (Goldberg PA, Inzucchi SE, Yale University, 11/04)
High-dose glucocorticoid treatment	<ul style="list-style-type: none"> – NPH insulin twice daily – long-acting insulin analogues in the morning or evening 	<ul style="list-style-type: none"> – normal insulin or short-acting insulin analogues before meals 	<ul style="list-style-type: none"> – normal insulin or short-acting insulin analogues on a sliding scale 	<ul style="list-style-type: none"> – glucocorticoids elevate the insulin requirement – insulin dose adjustment is needed especially after meals and 8–12 hours after glucocorticoid administration

Neutral protamine Hagedorn (NPH) insulin, delayed insulins with longer-lasting effect because insulin is bound to protamine, a basic protein; long-acting insulin analogues, insulin glargine and detemir; short-acting insulin analogues, insulin lispro, insulin aspart, and insulin glulisin; mixed insulins, fixed combinations of NPH insulin with normal or short-acting insulin; BW, body weight

TABLE 4

Stages of Chronic Kidney Disease (CKD) (modified from e24)

CKD stage	Creatinine clearance (mL/min)	Proteinuria	No proteinuria
1	>89	renal disease with normal renal function	normal
2	60–89	renal disease with mildly impaired renal function	mildly impaired renal function, but no renal disease
3	30–59	renal disease with moderately impaired renal function	renal disease with moderately impaired renal function
4	15–29	renal disease with severely impaired renal function	renal disease with severely impaired renal function
5	<15	chronic renal failure	chronic renal failure

seem reasonable to discontinue sulfonylureas temporarily before contrast studies, as these drugs are mainly eliminated through the kidneys.

High-dose glucocorticoid treatment

The insulin requirement increases during high-dose glucocorticoid treatment; in particular, the insulin dose must be adjusted postprandially and 8 to 12 hours after glucocorticoid administration. More detailed recommendations are given in *Table 3* and in references (8) and (9).

Coronary heart disease

The effect of near-normal glycemic control on the microvascular complications of type 2 diabetes (e.g., nephropathy and retinopathy) has been documented in large-scale studies (e8, e9). The data on macrovascular complications are inconsistent. Intensified blood-glucose reduction had no significant effect on the cardiovascular endpoints of the UKPD trial (e8), nor did intensified antihyperglycemic treatment significantly lower the frequency of macrovascular endpoints in the ADVANCE trial (e10). The ACCORD trial actually revealed increased mortality among the more intensively treated patients (e11). In the VADT trial, the two treatment groups did not differ in the frequency of cardiovascular events (e12). Meta-analyses of the large-scale endpoint trials have shown a significant advantage for more intensive glycemic control only with respect to non-fatal myocardial infarction (10). Further analysis indicates that excessive reduction of the HbA_{1c} concentration can be dangerous, particularly for elderly patients who have had diabetes for many years and for patients who have had a prior coronary event. Hypoglycemia is thought to induce catecholamine-mediated arrhythmias and other ECG changes (11). Thus, strict avoidance of hypoglycemia seems advisable in patients with coronary heart disease (CHD). Sulfonylureas and glinides should be used with caution in view of the danger of hypoglycemia and of potential interactions with cardiac sulfonylurea receptors (e13, e14). With regard to metformin, a subgroup analysis in the UKPD trial revealed a significant reduction of cardiovascular

endpoints among overweight patients (12). For patients with acute coronary ischemia, temporary discontinuation of oral hypoglycemic treatment is recommended, in view of the potential need for a radiological contrast study and the increased risk of lactic acidosis.

Dipeptidyl-peptidase-4 (DPP-4) inhibitors and glucagon-like-peptide-1 (GLP-1) analogues can be used for glycemic control with practically no risk of hypoglycemia (e15, e16). Small-scale clinical trials have shown improved cardiac performance in CHD patients after the administration of a DPP-4 inhibitor or during the infusion of native GLP-1 (e17, e18). Preliminary safety studies of the currently available DPP-4 inhibitors also suggest that these may lower the frequency of cardiovascular events (Lamanna C, et al. Dipeptidyl peptidase-4 inhibitors and cardiovascular events: a protective effect? European Association for the Study of Diabetes 2011 Meeting; Lisbon, Portugal. Abstract 244). These results still need to be validated in endpoint trials, and thus no recommendation can yet be given with regard to the use of these drugs in patients with CHD. In case of an acute coronary event, the recommendation is to stop all oral antidiabetic medication temporarily and switch to subcutaneous insulin administration (8). Current data do not support any general recommendation for intravenous therapy with insulin, glucose, and potassium (e19, e20).

Congestive heart failure

Congestive heart failure is at least twice as prevalent among patients with diabetes mellitus as in the normal population (13). Diastolic dysfunction frequently arises at an early stage of diabetes, often as early as the stage of reduced glucose tolerance (e21). Metformin is contraindicated for antidiabetic treatment in patients with advanced congestive heart failure (New York Heart Association [NYHA] stages 3 and 4) (7), because the inadequate pumping function of the heart promotes the accumulation of acid metabolites, leading to the risk of lactic acidosis (4). On the other hand, retrospective trials have shown a long-term survival advantage from metformin treatment in diabetics with congestive heart failure (14). Thus, metformin is recommended for use

TABLE 5

Restrictions on the use of oral antidiabetic drugs in patients with renal failure (RF) or hepatic insufficiency (HI), as of 10 January 2012 (7, 25)

Substance class	Drug	Dose adjustment in patients with renal failure (RF) or hepatic insufficiency (HI)	
Biguanides	Metformin	RF	check the serum creatinine concentration before starting treatment and annually in patients with normal renal function, 2–4 times per year in patients with impaired renal function; contraindicated in CKD stage 3 or above
		HI	contraindicated in overt HI; mild impairment of liver function is not a contraindication
Sulfonylureas	Glimepiride	RF	use with caution in RF; contraindicated in CKD stage 4 or above
		HI	contraindicated in overt HI; mild impairment of liver function is not a contraindication
Sulfonylureas	Glibenclamide	RF	use with caution in RF; contraindicated in CKD stage 4 or above
		HI	contraindicated in overt HI; mild impairment of liver function is not a contraindication
Sulfonylureas	Gliquidone	RF	use with caution in RF; contraindicated in CKD stage 4 or above
		HI	contraindicated in overt HI; mild impairment of liver function is not a contraindication
Sulfonylureas	Gliclazide	RF	use with caution in RF; contraindicated in CKD stage 4 or above
		HI	contraindicated in overt HI; mild impairment of liver function is not a contraindication
Glinides	Repaglinide	RF	dose adjustment with elevated AUC/t _{1/2} ; RF <i>per se</i> is not a contraindication
		HI	not recommended if there is any impairment of liver function; contraindicated in severe HI
Glinides	Nateglinide	RF	dose adjustment with elevated AUC/t _{1/2} ; RF <i>per se</i> is not a contraindication
		HI	no dose adjustment needed in mild to moderate HI; contraindicated in severe HI
Glitazones (TZDs)	Pioglitazone	RF	no dose adjustment needed with creatinine clearance over 4 mL/min; contraindicated in CKD stage 5
		HI	contraindicated if liver function is impaired (ALT >2.5 x upper limit of normal)
DPP-4 inhibitors	Saxagliptin	RF	in CKD stages 3 and 4, max. 2.5 mg/d; not recommended in CKD stage 5
		HI	no dose adjustment needed in mild to moderate HI; contraindicated in severe HI
DPP-4 inhibitors	Sitagliptin	RF	standard dose in CKD stages 1 and 2, dose reduction to 50 mg/d in CKD stage 3, dose reduction to 25 mg/d in CKD stages 4 and 5
		HI	no dose adjustment needed in mild to moderate HI; contraindicated in severe HI
DPP-4 inhibitors	Vildagliptin	RF	standard dose in CKD stages 1 and 2, dose reduction to 50 mg/d in CKD stages 3 and 4, dose reduction to 50 mg/d and use with caution in CKD stage 5
		HI	contraindicated if liver function is impaired (ALT or AST >3 x upper limit of normal)
GLP-1 agonists	Exenatide	RF	standard dose in CKD stages 1 and 2, conservative dose escalation in CKD stage 3, contraindicated in CKD stages 4 and 5
		HI	no dose adjustment needed in HI
GLP-1 agonists	Liraglutide	RF	standard dose in CKD stages 1 and 2, contraindicated in CKD stage 3 and above
		HI	contraindicated in patients with mild, moderate, or severe HI
Alpha-glucosidase inhibitors	Acarbose	RF	contraindicated in CKD stages 4 and 5
		HI	contraindicated in overt HI; mild impairment of liver function is not a contraindication
Alpha-glucosidase inhibitors	Miglitol	RF	contraindicated in CKD stages 4 and 5
		HI	no dose adjustment needed in HI
Insulin	Various insulins	RF	cautious dose adjustment in RF because of potentially slowed insulin degradation
		HI	cautious dose adjustment in RF because of potentially slowed insulin degradation

AUC, Area under the curve; t_{1/2}, half-life; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD, chronic kidney disease

FIGURE

Sliding scales		
1. select a rapidly-acting insulin (normal/old insulin)	2. set a glycemic target	3. set a correction factor
e.g., old insulin	e.g., 150 mg/dL	e.g., 1 IU / 30 mg/dL
4. measure the current blood glucose concentration	5. calculate the difference between the actual and target values	6. multiply the difference by the correction factor
e.g., 210 mg/dL	here: $210 \text{ mg/dL} - 150 \text{ mg/dL} = 60 \text{ mg/dL}$	here: $60 \text{ mg/dL} \cdot (1 \text{ IU} / 30 \text{ mg/dL}) = 2 \text{ IU}$

Sliding scales as an option for the temporary treatment of hospitalized patients with insulin

by diabetics with NYHA stage 1 and 2 congestive heart failure. As for sulfonylureas, glinides, and insulin, there are no general restrictions on the use of these drugs in diabetics with congestive heart failure. The physician should be mindful of the risk of hypoglycemic episodes and of fluid retention, which is occasionally seen under treatment with insulin (e22). Pioglitazone has been found in many trials to elevate the incidence of cardiac decompensation and is therefore contraindicated in patients with congestive heart failure (in any NYHA stage) (e23). GLP-1 analogues and DPP-4 inhibitors seem to have positive net effects on myocardial function (e16, e17) and may, therefore, be a good option for patients with congestive heart failure, although prospective endpoint trials on this question are entirely lacking. In cases of acute cardiac decompensation, temporary insulin treatment would appear to be the best option for in-hospital glycemic control (8); here, too, there is a lack of evidence from large-scale randomized trials and longitudinal studies.

Renal failure

Twenty to forty percent of patients with type 2 diabetes develop renal failure in the course of their disease (15). Renal failure is classified by chronic kidney disease (CKD) stages, as shown in *Table 4* (e24). As most oral antidiabetic drugs are eliminated through the kidneys, there are constraints on their use in patients with impaired renal function.

Metformin is contraindicated because of potential accumulation if the creatinine clearance is lower than 60 mL/min (4, 7, 16) but can be given to patients in CKD stages 1 and 2 as long as their renal function is monitored by laboratory testing two to four times a year. A Cochrane review found no significant increase in the frequency of lactic acidosis under treatment with

metformin (17). Some experts have suggested further liberalization of the glomerular-filtration-rate (GFR) cut-off value for metformin (e.g., to 45 mL/min), but this cannot be generally recommended, in view of the medicolegal consequences in the rare event that lactic acidosis does develop (e25).

The renally eliminated sulfonylureas can accumulate and cause dangerous hypoglycemia in patients with renal failure. This is especially true of the long-acting drugs glibenclamide and glimepiride; hypoglycemia can even arise several days after these drugs are discontinued. Thus, sulfonylureas are contraindicated in CKD stages 4 and 5 (4, 7, 16). The same contraindication applies for gliquidone, a sulfonylurea often given to patients with impaired renal function (7).

Glinides, on the other hand, are eliminated almost exclusively through the liver and are thus, after dose adjustment, suitable for use in advanced CKD stages (7).

Incretin-mimetic drugs and DPP-4 inhibitors can be used without any special restrictions by patients with renal failure in CKD stage 1 or 2 (7); exenatide can be used at a reduced dose in stage 3 as well (7), saxagliptin up to stage 4 according to current data (e26), sitagliptin and vildagliptin up to stage 5 (7, 25). Restrictions on the use of oral antidiabetic drugs are summarized in *Table 5*.

Insulin treatment is generally recommended for patients with advanced renal failure. It should be borne in mind, however, that the effect of insulin can be prolonged in renal failure because of reduced insulin clearance, while patients with renal failure may simultaneously have increased resistance to insulin (18). The insulin dose usually has to be lowered in the setting of renal failure (19), but there are no uniform recommendations on this matter, and the dosage must be carefully titrated. Treatment with short-acting insulin may be advantageous for patients with renal failure (e27).

Hepatic disease

Although diabetes is more common in patients with impaired liver function, there are hardly any data on the treatment of diabetes in such patients. Thus, antidiabetic drugs are chosen mainly on the basis of their side-effect profiles. No more than a few cases of hepatotoxic side effects have been reported for metformin (e28), but the risk of lactic acidosis may be higher in the setting of impaired liver function, and metformin is therefore contraindicated for patients with advanced liver failure (4, 7, 16). On the other hand, in the much more common cases of hepatopathy without liver failure, metformin actually appears to have a beneficial effect on hepatic metabolism (e29–e32). As regards treatment with sulfonylureas, glinides, and insulin, one should bear in mind that there is an increased risk of hypoglycemia because of diminished hepatic gluconeogenesis. Moreover, glinides are eliminated almost exclusively through the liver and are thus contraindicated in the setting of impaired liver function (4, 7). Sulfonylureas are contraindicated in advanced liver failure (4, 7). Data are currently lacking on antidiabetic treatment

with incretin-mimetic drugs and DPP-4 inhibitors in the setting of coexistent liver disease. Patients with moderately impaired liver function can take sitagliptin or exenatide (e33, e34). Liraglutide is considered to be contraindicated in the setting of impaired liver function because of a lack of data from clinical studies (7). In clinical studies of vildagliptin, high doses caused elevation of hepatic transaminases in a small number of patients; thus, this drug is not recommended for patients with impaired liver function (7). All oral antidiabetic agents are contraindicated in patients with advanced liver disease. Restrictions on the use of oral antidiabetic drugs are summarized in *Table 5*. As can be seen, for many patients with advanced liver disease, insulin treatment is the only available option for glycemic control. No systematic studies have yet been devoted to the question whether a prandial or basal insulin regimen is better in this setting.

Overview

In view of the many restrictions on the use of oral antidiabetic drugs that have been described in the foregoing paragraphs, temporary insulin treatment remains the only practical means of glycemic control for many hospitalized patients with type 2 diabetes. To this end, sliding scales can be used, supplemented by the additional administration of a fixed number of units of insulin with the main meals of the day and/or long-acting insulin analogues given once or twice daily (9, 16). These treatment options are summarized in the *Figure*. Detailed recommendations on the concrete implementation of temporary insulin treatment can be found, for example, in reference (16) (in German). In a prospective, randomized multicenter trial, base-bolus therapy was found to provide better glycemic control than a sliding scale (20). For long-term treatment, the once-daily administration of a long-acting insulin analogue seems to lead to fewer hypoglycemic episodes than the administration of short-acting insulin three times a day, while yielding comparable HbA_{1c} values (21, 22). In a recent trial, a combination of rapid- and long-acting insulin analogues was found to have no therapeutic advantage over neutral protamine Hagedorn (NPH) human insulin in the inpatient setting (23).

Antidiabetic treatment in hospitalized patients thus differs in many respects from the treatment of outpatients. The special accompanying circumstances and comorbidities necessitate flexible, individualized glycemic management in the hospital.

Conflict of interest statement

Professor Meier has received lecture honoraria and consulting fees from the following companies: Astra Zeneca, Berlin-Chemie, BMS, Boehringer-Ingelheim, Eli Lilly, MSD, NovoNordisk, Novartis, Roche, and Sanofi-Aventis. He has received reimbursement of congress participation fees and travel expenses from MSD, NovoNordisk, and Sanofi-Aventis. MSD, NovoNordisk, and Sanofi-Aventis support research projects that he initiated. Dr. Breuer has received reimbursement of congress participation fees and travel expenses from Sanofi-Aventis and NovoNordisk.

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Translated from the original German by Ethan Taub, M.D.

KEY MESSAGES

- The treatment of diabetes in the hospital differs markedly from outpatient treatment in terms of the goals of treatment and the particular pharmacotherapeutic measures that are taken.
- In acutely ill patients, the blood glucose concentration should be 140–180 mg/dL. For clinically stable patients on non-intensive-care hospital wards, the target values are below 140 mg/dL in the fasting state and below 180 mg/dL postprandially.
- A main goal of inpatient glycemic therapy is the strict avoidance of hypoglycemia.
- The choice of drug treatment must take account of any relevant accompanying illnesses, pending invasive procedures, prolonged fasting periods, and acute impairments of renal and/or hepatic function.
- For many diabetic patients in the hospital, temporary insulin treatment in the form of a sliding scale or base-bolus therapy is a good therapeutic option for glycemic control.

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REVIEW ARTICLE

Inpatient Treatment of Type 2 Diabetes

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