

Type 2 diabetes

Reducing hypoglycaemia



Key messages

- Hypoglycaemia is common in people with type 2 diabetes on insulin and/or sulfonylureas.
- Hypoglycaemia can cause injury from falls and accidents, arrhythmias, heart attack and impaired cognition. It may be fatal and is an important cause of hospital admission.
- **Hypoglycaemia is increased in older people 65 years or more.**
Low HbA1c <53 mmol/mol, reduced renal function, co-morbidities or interacting medications increase these risks.
- **NICE recommends an individualised approach to diabetes care with more relaxed HbA1c targets in older people at higher hypoglycaemia risk.**
- **Consider HbA1c targets 64 to 75 mmol/mol or more for people at increased risk of hypoglycemia.**
- In people under age 80 years, ensure systolic blood pressure is <140 mmHg and atorvastatin 40/80mg are optimally used.

Aim of the guideline

This guidance is primarily focussed on people over the age of 65 years with type 2 diabetes who are on insulin and/or sulfonylureas who are most at risk, but it applies also to adults at-risk at younger ages.

It is intended to minimise harm from hypoglycaemia and optimise patient benefit from antihypertensives and statins.

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This document reflects some of the views expressed at a meeting in Newham in 2015 to discuss recent guidance on reducing hypoglycaemia. The meeting included a range of stakeholders including CCG prescribing advisors, GPs, hospital consultants and specialist nurses.

This document was written by John Robson.

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CEG information on the website at <http://www.blizard.qmul.ac.uk/ceg-home.html>

Any queries regarding this document should be addressed to CEG at

ihse-ceg-admin@qmul.ac.uk

58 Turner St

London E1 2AB

Review hypoglycaemia risk and optimise CVD benefit

Is this patient on a sulfonylurea or insulin?

Is patient 65 years or older with HbA1c < 53 mmol/mol or other risk factors for hypoglycaemia?§

**Consider more relaxed targets
HbA1c 64 -75 mmol/mol**

**Option to reduce insulin or SU?
Improved self-management?**

**Is control of CVD risk factors optimal?
Is patient on Atorvastatin 40mg or more? Is systolic BP below 140mmHg*?**

§ Older age, renal impairment, impaired cognition, interacting medicines - See oveleaf for full details
*In people age 80 years or more or frailty, systolic pressures of 150 mmHg may be more appropriate

Risks and harms of diabetes treatments

	HbA1c lowering (absolute)*	BENEFITS		HARMS		
		Cost effective CVD mortality reduction	Reduction in CVD events	Weight gain	Hypoglycaemia	Adverse Effect
Metformin	1.5%*	No	Possible	2kg Loss	Rare on monotherapy	GI symps
Sulfonylureas	1.5%*	No	No	2kg-4kg Gain	High	
Pioglitazone	1%*	No	No	3kg-4kg Gain	Incscd+SU/Ins	HF, # risk
DPP4	<1%	No	No	No change	Incscd+SU/Ins	GI symps
GLP-1	<1%	No	No; Evidence contested	2Kg Loss	Incscd+SU/Ins	GI symps
SLGT2	<1%*	No	Empagliflozin	2kg Loss	Low or reduced	
Insulin	>2%*	No	Uncertain	4Kg Gain	Highest	

*HbA1c reduction gets less over time. Most people increase to pre-treatment levels within 5 years (New agents unknown long-term)

New guidance on hypoglycaemia

Concerns about harms from glycaemic treatments for type 2 diabetes at older ages have led to revised guidance from NICE¹ and organisations in both Europe and the USA.^{2,3,4}

These advise that HbA1c targets of less than 58 mmol/mol may not be appropriate for people at older ages, those with impaired renal function, co-morbidities, limited life expectancy, interacting medication, previous hypoglycaemia or inability to self-manage treatment.

Hypoglycaemia is mainly related to insulin and sulfonylurea use

Review of patients with type 2 diabetes on insulin or sulfonylureas is recommended to reduce hypoglycaemic risk and maximise CVD benefit with optimal blood pressure control and statin use.

Individualise treatment, with HbA1c targets above 64 mmol/mol in people at increased risk of hypoglycaemia.

Where life expectancy is short, less stringent HbA1c targets may be appropriate.

About this guideline

This guideline summarises hypoglycaemic risk and the use of the APL-Hypo tool to identify people at high risk.

The APL-hypo tool is a simple way to identify people at increased risk. We shall evaluate the effect of this programme on HbA1c, recorded hypoglycaemia and diabetes related admissions to hospital.

This guidance outlines steps to identify people at risk of hypoglycaemia and management to avoid this. Reduction or cessation of treatment where appropriate, is advised in a stepped and monitored clinical context.

Targets

European and American guidance^{2,4} recommend more relaxed HbA1c targets of 64-75 mmol/mol (8-9%) for older people at risk of hypoglycaemia. In some people with limited life expectancy - for example over age 80 years with co-morbidity in the final years of life - levels of 86 mmol/mol (10%) may be appropriate.

NICE Guidance

NICE guidance¹ states ... “Adopt an individualised approach to diabetes care that is tailored to the needs and circumstances of adults with type 2 diabetes.”

- Take account of patient personal preferences
- Co-morbidities
- Risks from polypharmacy
- Ability to benefit from long-term interventions due to multimorbidity limiting life expectancy.
- Reassess the person’s needs and circumstances at each review. Think about whether to stop any medicines that are not effective

NICE and targets

NICE guidance states ...

“Consider relaxing the target HbA1c level on a case-by-case basis, with particular consideration for people who are...”

- older or frail
- unlikely to achieve longer-term risk reduction benefits; for example, people with a reduced life expectancy
- for whom tight blood glucose control poses a high risk of the consequences of hypoglycaemia; (people at risk of falling; impaired awareness of hypoglycaemia; drivers or people who work with machinery)
- people with significant co-morbidities

Background

In type 2 diabetes, the use of sulfonylureas and insulin to reduce HbA1c to less than 58 mmol/mol has been associated with increased mortality.^{5,6} In older people, there is particular concern that intensive treatments including insulin and sulfonylureas, increase the risk of hypoglycaemia and that the negative impact of treatment, particularly with insulin, additionally reduces quality of life.^{7,8}

Recent NICE guidance recommends more relaxed targets for older people with type 2 diabetes at high risk of hypoglycaemia. Similar recommendations are supported in European and American guidance.

There is also considerable undertreatment of cardiovascular risk through suboptimal use of antihypertensives and high intensity statins.^{9,10} In short, often expensive glycaemic medicines are overused and cheap CVD treatments are underused in many older patients.

Concern about these risks and a move to more relaxed HbA1c targets, mean that a substantial proportion of people over 65 years on sulfonylureas and/or insulin require a review of current treatment. These reviews are an opportunity to minimise hypoglycaemia and also to consider whether optimal CVD benefit is being obtained.

How big is the problem?

In type 2 diabetes in patients on insulin and/or sulfonylureas, hypoglycaemia is a major problem.^{11,12} Patient surveys confirm that clinical reports of hypoglycaemia are the tip of a much larger burden of unreported episodes, more severe in users of insulin than sulfonylureas.^{13,11} 80% of community hypoglycaemic episodes are self-managed.

Severe hypoglycaemia is the second commonest cause of hospital admission for drug related adverse events.

There are twice as many admissions for hypoglycaemia as for hyperglycaemia. In people with type 2 diabetes on sulfonylureas or insulin monitored over a 3 month period, there were an average of 7 hypoglycaemic events per person (both asymptomatic and symptomatic).¹¹ Hypoglycaemia is also associated with an increased risk of CVD events or death, particularly in people with pre-existing CVD.¹⁴⁻¹⁷

Patient factors causing hypoglycaemia²⁷

Hypoglycaemia is more common:

- at older ages
- multiple co-morbidities
- impaired cognition or dementia
- renal impairment
- limited health literacy
- social deprivation
- interacting common medicines

Hypoglycaemia may also have behavioural antecedents. Missing meals, fasting or irregular tablet taking are common. Errors in insulin dosing are frequent.

Renal factors causing hypoglycaemia

Insulin and sulfonylureas are excreted by the kidney and reduced renal function increases hypoglycaemia. Diabetes is the commonest cause of impaired renal function.²⁸ Around 40% of patients over the age of 65 years with type 2 diabetes have an estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73m² (stage 3 chronic kidney disease).^{29,30} Hospitalisation is related to insulin use, age, presence of chronic kidney disease and hypoglycaemia.³¹

In the USA a third of patients with type 2 diabetes on insulin or sulfonylureas were over 75 years or had renal impairment. Of these, 50% had an HbA1c of less than 53mmol/mol and 11% less than 42 mmol/mol.⁸ East London has similar figures.

Drug interactions causing hypoglycaemia

Common medications substantially increase risks of hypoglycaemia.³²

- Cotrimoxazole, ciprofloxacin/quinalones, erythromycin/macrolides, antifungals.
 - Tramadol increases hypoglycaemia risk fourfold.³³
 - SSRIs
 - Beta blockers
 - Aspirin, gemfibrozil and warfarin
- Alcohol is also an important cause of hypoglycaemia.

Hypoglycaemia risks and the APL-Hypo tool

DRUG INTERACTION	
Insulin treatment	Red
Erythromycin, clarithromycin, azithromycin	Red
Ciprofloxacin and other quinolones	Red
Metronidazole, itraconazole, ketoconazole	Red
Co-trimoxazole	Red
Isoniazid	Red
Tramadol	Red
PPIs	Yellow
SSRI/tricyclic antidepressant	Yellow
Aspirin	Yellow
Beta-blockers	Yellow
SOCIAL	
Dementia	Red
Learning disability	Red
SMI	Red
Palliative care	Red
Housebound/nursing home	Yellow
Alcohol >6U/week	Yellow
Age 65-74 years	Yellow
Age 75 years and older	Red
HbA1c (latest)	
HbA1c <48 mmol/mol	Red
HbA1c 48-57 mmol/mol	Yellow
CO-MORBIDITY	
eGFR <30 ml/min (latest)	Red
eGFR 30-59 ml/min (latest)	Yellow
IHD/Stroke/TIA/HF/AF/PAD/COPD	Yellow
Previous hypoglycaemia	Red
Falls	Yellow
Low BMI <20	Yellow

APL-Hypo tool

At older ages, hypoglycaemic risk is the norm, not the exception in patients on sulfonylureas or insulin.

The APL-Hypo (Active Patient Link) tool, is based upon studies in people on sulfonylureas or insulin showing relative risks of different factors;

Highest risks score = 2 (RED)
 Lesser risks score = 1 (AMBER)

Ranking these total scores from highest to lowest, enables the clinician to select patients at highest risk for the earliest review.

These scores have not been derived from a predictive model and do not predict hypoglycaemia in any individual patient.

The ranking is simply intended to provide a visual summary of identified risks, to indicate which patients may be most appropriate for a review of treatment to reduce hypoglycaemic risk.

The APL-Hypo tool extracts the relevant information from the GP health records and displays them in an easy to use format.

Those at highest risk can be called first for diabetes medication review.

In a typical CCG more than half the patients over 65 years on sulfonylureas or insulin have 3 or more risks in the categories listed

- drug interaction
- social factors
- low HbA1c
- co-morbidity

Why use intensive treatments?

Why does this patient require more intensive treatment?

- to reduce the risk of hyperglycaemic complications?
- or to reduce micro or macrovascular CVD?
- reduce thirst or polyuria?

There is little evidence that more intensive treatment with sulfonylureas or insulin in older people with established diabetes improves CVD outcomes.

Neither insulins or sulfonylureas reduce cardiovascular or total mortality. There is limited and contested evidence that in younger people with recent onset diabetes there may be a reduction in non-fatal CHD and small improvements in microvascular disease. There is no such evidence in older people and hypoglycaemia is a major and frequent cause of adverse events, in this age group.²⁰⁻²⁷

Nevertheless, there are older patients where hyperglycaemia, often in conjunction with polyuria or thirst, is a major issue. Progressive beta cell failure is a feature of longstanding type 2 diabetes. In some patients the only therapeutic option will therefore be insulin or sulfonylurea therapy. The aim in such patients is to improve glucose control whilst minimising hypoglycaemia risk.

Factors influencing treatment

20% of older people with type 2 diabetes receive intensive treatment putting them at risk of hypoglycaemia. There are a range of issues to be considered when reviewing patients for risk of hypoglycaemia.³⁶

PATIENT PREFERENCE particularly avoidance of injections should be a major factor in the treatment decision, as is the need for daily blood glucose-testing.⁷ Additional tablets may also be a critical factor where polypharmacy is the norm.

Decision making is complex and requires an extended conversation to set out the options, including the impact of monitoring and the potential gains and downsides of treatments.

If the choice is between controlling blood pressure and starting a statin, versus tighter control of HbA1c below 75 mmol/mol, then CVD gains will provide greater patient benefit.

KIDNEY DISEASE 30% of the diabetes population over 65 years have an eGFR <60 ml/min and 10% have eGFR <30 ml/min. Renal function declines at older ages and drug excretion declines with it, increasing the intensity and duration of hypoglycaemic effects.^{28,29}

Factors influencing treatment

PREVIOUS HYPOGLYCAEMIA asymptomatic or severe, requiring help from a third person, or causing injury or hospitalisation, predicts higher likelihood of recurrence.

DEMENTIA, POOR COGNITION OR HEALTH LITERACY or those on insulin known to have dosing difficulties or hypoglycaemia unawareness.

Overall HbA1c control should be considered alongside the patients ability to self-manage including self-monitoring of blood glucose.

FRAILITY or low Body Mass Index <20

DURATION >10 YRS ON INSULIN

INTERACTING DRUGS AND POLYPHARMACY including common antibiotics, tramadol and SSRI.³⁰⁻³²

Treatment choices

It is beyond the scope of this guidance to present more than a cursory sketch of relevant issues. If medicines are reduced or stopped, patients should be appropriately monitored. Individual management should be considered with the patient and their carers. Experience in more complex cases will be gained through clinical dialogue including MDT discussions. Treatment reductions should be stepped and reviewed. (*see decision aids at end of this guidance*)³⁷

Patients at high risk of hypoglycaemia where HbA1c is below 53 mmol/mol and who have other risk factors, should be among the first to have their treatment reviewed (see APL tool).

Sulfonylureas

Shorter acting sulfonylureas such as gliclazide, glipizide or glimepiride are preferred to long acting glibenclamide. However these may still produce hypoglycaemia 24 hrs after ingestion.

There is no justification for using tolbutamide. It is expensive (10 times the cost of gliclazide/glipizide) and the only controlled trial (UGDP 1970) was stopped early because of increased CVD mortality.

Sulfonylureas lower HbA1c by ~15 mmol/mol and are associated with increased hypoglycaemia.

Treatment choices

Insulin, sulfonylureas and pioglitazone

Where long acting insulin is used, human insulin (Insulatard, Humulin, Insuman) is preferred to long acting analogue insulins (Detemir, Glargine, Degludec) because these analogue insulins are more expensive and confer only marginal benefits. Insulin and sulfonylureas have not been shown to reduce CVD mortality.

Oral glucose lowering drugs initially lower HbA1c by 5 to 15 mmol/mol. This reduction lessens with time and by 5 years is no longer apparent.

Pioglitazone, insulin, and sulfonylureas cause weight gain of 2-4 kg.

Up until 2016 newer agents also showed no reduction in CVD mortality.

The 2005 PROactive pioglitazone trial was not significant for the primary outcome and a 20% increase in heart failure offset gains from reduced non-fatal CVD events. Hypoglycaemia is more frequent on pioglitazone as are fractures.

Newer drugs

In 2016 the oral SGLT2 empagliflozin (EMPA-REG) trial showed a 38% relative reduction in CVD mortality and a 32% relative reduction in all cause mortality. Decline in renal function may also be improved. Absolute reduction in HbA1c was 5 mmol/mol falling to 3 mmol/mol after 3 years. Hypoglycaemia was not increased. Cost approx. £450 PA. The study population had a very high baseline CVD 10yr risk of 44%. (*NEJM June 2015*). It is estimated it would cost £73,000 to prevent one CVD event with empagliflozin.³⁸

The 2016 LEADER trial of subcutaneous liraglutide reduced CVD death by 22% and all cause mortality by 15%. HbA1c was reduced by 4 mmol/mol. Serious hypoglycaemia reduced from 3.3% in controls vs 2.2% in intervention. However, insulin and sulfonylurea use in controls was much greater than in the intervention group which may increase CVD and adverse events in controls. Discontinuation due to adverse events was greater in the intervention group (9.5% vs 7.3%). GI tract symptoms were common, including gallstones. Cost £936-£1400 PA (*NEJM June 2016*). These newer agents are not cost-effective in respect of CVD reduction and systematic treatment bias may have influenced LEADER results.

The least worst option?

If the aim is simply to reduce blood glucose to achieve HbA1c below 75 mmol/mol, then any of the choices are available, but the newer agents only reduce HbA1c by 5 mmol/mol or less at much higher cost than older agents. See NICE treatment ladder.

In addition, the newer agents in conjunction with either sulfonylureas or insulin, may further increase the hypoglycaemic risk.

Patient wellbeing is a major issue, particularly at older ages when the burden of co-morbidity and polypharmacy is common. Additional diabetes medication causes marked declines in wellbeing, particularly those requiring frequent self-testing and insulin injections. Reduced wellbeing is usually more important than claimed potential gains in life expectancy.⁷

Avoidance of injections and frequent self-testing make insulin the least favoured patient choice. However, for those requiring more intensive glucose lowering, human insulin is often the only effective option to reduce uncontrolled glycaemia.

Long acting insulin costs around £250 per year and where glycaemic control is difficult, may give greater flexibility than fixed dose regimes. Insulin is associated with more hypoglycaemia and more weight gain than any other agent.

Hypoglycaemia can also occur in people with high HbA1c because of glucose variability, particularly those on insulin.

The vast majority of patients would prefer oral drugs and both pioglitazone or gliclazide are cheap, non-invasive and in the context of higher HbA1c values probably less likely to cause hypoglycaemia than insulin.

Given the choice, patients may also consider oral glipitins although gastrointestinal side effects are quite common. The cost of gliptins is more than 10x that of gliclazide or pioglitazone at around £380 per year. They are not cost-effective for CVD reduction and reduce HbA1c by only 3 mmol/mol. Glutides, given by injection once or twice a day, cost even more at around £1000 PA. None of these newer drugs including SGLT2 agents are more effective in lowering HbA1c than pioglitazone or gliclazide.

Decision support

The problem for treatment choices arises when older people with type 2 diabetes of more than 10 years duration have an HbA1c above 75 mmol/mol despite optimal advice on diet, physical activity and optimal doses of metformin - what should be added next?

In a patient age 70 years old with type 2 diabetes, BMI 30, systolic blood pressure 146mmHg, total cholesterol 6mmol/l and HDL 1 mmol/l.

This persons chance of dying or having a fatal or non-fatal heart attack or stroke in 10 years is 20%-40% estimated by QRisk2 (white-SouthAsian).

Statins, hypertension and glycaemic treatment

Anti-hypertensives reduce CVD risk by at least 25% and high intensity statins (atorvastatin 40mg or 80mg) by 30%. Combine the two and risk is reduced by around 50%.

In other words, if 100 people like this 70 year old, were treated for 10 years, heart attack or stroke would be reduced by half, which would prevent...

- **10 CVD events in women and 20 in men; depending on ethnic group and other risk factors. Serious adverse events are unusual.**

BP targets of systolic <140 mmHg are appropriate in most adults with type 2 diabetes. In those over age 80 years or who are frail, targets of less than 150 mmHg may be more appropriate.

In contrast, the risks of anti-glycaemic medicines outweigh benefits. On the most optimistic estimate of benefit, based on anti-glycaemic treatment in younger people with recent onset diabetes, **100 people over 65 years treated for 10 years would:**

- prevent heart attacks in 7 men and 3 women.
- cause severe hypoglycaemia in 10 or more people

In fact most reviews indicate that in older people with established diabetes there is little or no CVD benefit. Without overly optimistic assumptions of CVD benefit, intensive treatment is more likely to cause net harm than benefit.⁷

Conclusion

There are a large group of over 30% of older patients with type 2 diabetes currently on sulfonylureas and insulin who can be identified by their low HbA1c < 53 mmol/mol, poor renal function and/or other risk factors as having high risk of hypoglycaemia.

In a CCG that is about 600 patients, averaging 15 per practice. Sulfonylureas and insulin in patients at increased risk of hypoglycaemia should be reviewed to reduce this risk. This medication review is also an opportunity to optimise blood pressure management and ensure appropriate treatment with atorvastatin 40-80 mg.

The treatment decisions about glycaemic medications are complex and should take real account of patient preferences. For most of them the CVD benefits are very small and are likely to be outweighed by harms. NICE decision aids are given at the end of this guidance.

Gains from optimal treatment

Less intensive treatment with insulin/SU	Impact
CVD, renal or visual risks	Little if any change
Risk of severe hypoglycaemia	Risk reduced
Common side effects: Weight gain, nausea, diarrhoea	May be reduced
High risk of both hyperglycaemic complications and also hypoglycaemia?	highly variable 'brittle' diabetes requires detailed review
Optimal BP <140 mmHg and atorvastatin 40/80mg	Reduced stroke and IHD

Case study 1

Prolonged hypoglycaemia in the elderly

An 89-year-old woman was admitted to hospital from a nursing home with a 12 hour history of drowsiness and inability to eat or drink, progressing to an unrousable state.

She had had well controlled type 2 diabetes mellitus and associated corticosteroid use, for which she had been prescribed glimepiride 0.5 mg daily 2 months previously. The last dose was given on the morning of hospital admission. She was taking multiple other medications for co-morbid conditions.

A low dose of long acting morphine had been commenced 2 days earlier for painful arthritis. A glucometer reading taken in the nursing home on the morning of hospitalisation was 4.1 mmol/L.

The ambulance officers transporting her to hospital had recorded a “Lo” glucometer reading and administered 25 mL of 50% glucose. Within 5 minutes, a repeat glucometer reading was 14.7 mmol/L. On arrival at hospital the woman was opening her eyes and responding appropriately to pain, but not verbalising. Her Glasgow Coma Score was 9/15.

In A&E, a glucometer reading showed 4.8 mmol/L, but shortly afterwards her venous serum glucose concentration was 1.3 mmol/L. Results of a cerebral CT scan were unremarkable. Over the next 15 hours, there were six more glucometer readings with levels < 3.5 mmol/L, including readings of 0.6mmol/L and 1.8 mmol/L (18 and 27 hours after the last dose of glimepiride, respectively). Despite a total of 250 mL of 50% glucose in eight bolus doses and a 5% glucose infusion commenced at admission and continued throughout hospitalisation, her level of consciousness deteriorated. She died 18 hours after presentation.

Veitch P, Cifton-Bligh RJ MJA 2004; 180: 84

Learning points

Presentation of hypoglycaemia in older people may be atypical.

The classical autonomic adrenergic symptoms and signs of hypoglycaemia may not be evident.

Neuroglycopenic features, such as drowsiness or confusion, may dominate the picture.

Case study 2

Severe hypoglycemia due to fasting

A 56 year-old man with type 2 diabetes on insulin who had been fasting during Ramadan was admitted through the Accident and Emergency department with severe hypoglycemia. On arrival at his home, paramedics noted a capillary blood glucose level of 2.2 mmol/L. On admission to hospital, computed tomography of the brain showed evidence of a new right cortical infarct. A working diagnosis was made of acute stroke secondary to hypoglycemia, complicated by aspiration pneumonia.

Intravenous glucose infusion and antibiotics were commenced, with no improvement in consciousness level. He was admitted to the stroke unit, and his condition improved over 10 days. He required rehabilitation and was discharged after four weeks with a residual mild left-sided weakness.

When questioned, he stated that he was advised by his diabetes nurse not to fast, but had decided to do so anyway, reducing his insulin dose to what he thought was a safe level.

It is recommended that all Muslim patients with diabetes undergo a pre-Ramadan assessment, and if deemed to be high-risk they should be advised not to fast. Those who plan to fast will require individualized advice on adjusting therapy when fasting for Ramadan.

Chowdhury T. Diabetic Hypoglycemia October 2011, Volume 4, Issue 2: page 11-13 (both Case Studies have been edited).

Further advice

Where treatment decisions are complex, discussion with colleagues at MDTs or consultant referral may provide further learning opportunities for optimal management.

Oral or IV glucose is the initial treatment of choice for hypoglycaemia.

Severe hypoglycaemia episodes may persist for 24hrs despite initial treatment.

There is no role for glucagon in sulfonylurea induced hypoglycaemia.

Glucagon is the first-line treatment for severe hypoglycemia in insulin-treated patients

References

1. NICE. Type 2 diabetes in adults: management: National Institute for Health and Care Excellence 2015. nice.org.uk/guidance/ng28 Accessed 3/12/2015
2. Sinclair AJ, et al. European Diabetes Working Party for Older People 2011 clinical guidelines for type 2 diabetes mellitus. Executive summary. *Diabetes Metab* 2011;37 Suppl 3:S27-38.
3. Inzucchi SE, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012;35:1364-79.
4. American Geriatrics Society Expert Panel on Care of Older Adults with Diabetes M, Moreno G, Mangione CM, Kimbro L, Vaisberg E. Guidelines abstracted from the American Geriatrics Society Guidelines for Improving the Care of Older Adults with Diabetes Mellitus: 2013 update. *J Am Geriatr Soc* 2013;61:2020-6.
5. Currie CJ, et al. Survival as a function of HbA1c in people with type 2 diabetes: a retrospective cohort study. *The Lancet* 2010;375:481-89.
6. Berard E, et al. 14-year risk of all-cause mortality according to hypoglycaemic drug exposure in a general population. *PLoS One* 2014;9:e95671.
7. Vijan S, et al. Effect of patients' risks and preferences on health gains with plasma glucose level lowering in type 2 diabetes mellitus. *JAMA internal medicine* 2014;174:1227-34.
8. Tseng CL, et al. Assessing potential glycemic overtreatment in persons at hypoglycemic risk. *JAMA internal medicine* 2014;174:259-68.
9. Jones NR, et al. Factors associated with statin treatment for the primary prevention of cardiovascular disease in people within 2 years following diagnosis of diabetes in Scotland, 2006-2008. *Diabet Med* 2014;31:640-6.
117. Roumie CL, et al. Association between intensification of metformin treatment with insulin vs sulfonylureas and cardiovascular events and all-cause mortality among patients with diabetes. *JAMA* 2014;311:2288-96.
10. Cooney MT, et al. Determinants of risk factor control in subjects with coronary heart disease: a report from the EUROASPIRE III investigators. *European journal of preventive cardiology* 2013;20:686-91.
11. Wendel CS, et al. Incidence of non-severe hypoglycaemia and intensity of treatment among veterans with Type 2 diabetes in the USA: a prospective observational study. *Diabet Med* 2014.
12. Monami M, et al. A meta-analysis of the hypoglycaemic risk in randomized controlled trials with sulphonylureas in patients with type 2 diabetes. *Diabetes Obes Metab* 2014;16:833-40.
13. Mitchell BD, et al. Hypoglycaemic events in patients with type 2 diabetes in the United Kingdom: associations with patient-reported outcomes and self-reported HbA1c. *BMC Endocr Disord* 2013;13:59.
14. Phung OJ, et al. Sulphonylureas and risk of cardiovascular disease: systematic review and meta-analysis. *Diabet Med* 2013;30:1160-71.
16. Currie CJ, et al. Mortality and other important diabetes-related outcomes with insulin vs other antihyperglycemic therapies in type 2 diabetes. *J Clin Endocrinol Metab* 2013;98:668-77.
19. Bonds DE, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. *BMJ* 2010;340:b4909.
18. Huang ES, et al. Patient perceptions of quality of life with diabetes-related complications and treatments. *Diabetes Care* 2007;30:2478-83.
20. Zoungas S, et al. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med* 2010;363:1410-8.
21. Whitmer RA, et al. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. *JAMA* 2009;301:1565-72.
22. Huang ES, et al. Rates of complications and mortality in older patients with diabetes mellitus: the diabetes and aging study. *JAMA internal medicine* 2014;174:251-8.
23. Amiel SA, et al. Hypoglycaemia in Type 2 diabetes. *Diabet Med* 2008;25:245-54.
24. Signorovitch JE, et al. Hypoglycaemia and accident risk in people with type 2 diabetes mellitus treated with non-insulin antidiabetic drugs. *Diabetes Obes Metab* 2013;15:335-41.
25. Hemmingsen B, et al. Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. *BMJ* 2011;343:d6898.
26. Boussageon R, et al. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. *BMJ* 2011;343:d4169.
27. Berkowitz SA, et al. Low socioeconomic status is associated with increased risk for hypoglycemia in diabetes patients: the Diabetes Study of Northern California (DISTANCE). *J Health Care Poor Underserved* 2014;25:478-90.
28. Cavanaugh K. Diabetes Management Issues for Patients with Chronic Kidney Disease. *Clinical Diabetes* 2007;25:7.
29. Middleton RJ, et al. The unrecognized prevalence of chronic kidney disease in diabetes. *Nephrol Dial Transplant* 2006;21:88-92.
30. Bailey RA, et al. Chronic kidney disease in US adults with type 2 diabetes: an updated national estimate of prevalence based on Kidney Disease: Improving Global Outcomes (KDIGO) staging. *BMC Res Notes* 2014;7:415.
33. Khalid JM, et al. Rates and risk of hospitalisation among patients with type 2 diabetes: retrospective cohort study using the UK General Practice Research Database linked to English Hospital Episode Statistics. *Int J Clin Pract* 2014;68:40-8.
32. Parekh TM, et al. Hypoglycemia after antimicrobial drug prescription for older patients using sulfonylureas. *JAMA internal medicine* 2014;174:1605-12.
33. Fournier JP, et al. Tramadol use and the risk of hospitalization for hypoglycemia in patients with noncancer pain. *JAMA internal medicine* 2015;175:186-93
34. Montori V. Selecting the right drug treatment for type 2 diabetes *BMJ* 2016;352:i1663 doi: 10.1136/bmj.i1663
35. Huang ES. Management of diabetes mellitus in older people with comorbidities. *BMJ* 2016;353:i2200.
36. McCoy R et al. Intensive Treatment and Severe Hypoglycemia Among Adults With Type 2 Diabetes *JAMA Intern Med.* doi:10.1001/jamainternmed.2016.2275
37. Yudkin JS et al. Sharing decisions about preventive treatment. *BMJ* 2016: June; 488-489.
38. Naci H, Basu S, Yudkin JS. Preventing cardiovascular events with empagliflozin: at what cost? *The lancet. Diabetes & endocrinology* 2015;3:931.

Resources for decision support

<http://chd.bestsciencemedicine.com/calc2.html>
<https://www.nice.org.uk/guidance/ng28/resources>
<https://diabetesdecisionaid.mayoclinic.org/>



Centre for Primary Care and Public Health
Barts and The London School of Medicine and Dentistry
Yvonne Carter Building
58 Turner Street
London E1 2AB
Tel: 020 7882 2553 Fax: 020 7882 2522
email: ihse-ceg-admin@qmul.ac.uk
website: www.blizard.qmul.ac.uk/ceg-home.html