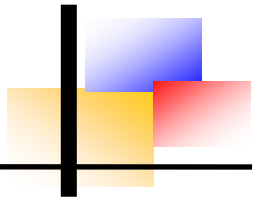
Pan Mersey
Adult Diabetes Management Guidelines
2014-2016 v18c



Title	Adult Diabetes Management Guidelines 2014-2016
Authors	Kevin Hardy on behalf of Mersey Diabetes Community
Purpose	Diabetes management guidance, primarily for non-specialists
Reference	Pan Mersey Diabetes Guidelines2014-16v18c.doc
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Full Review date	January 2016
Contact	Email kevin.hardy@sthk.nhs.uk or call 01744646497
Format	Electronic
Evidence-base	See Introduction and Topics & full NICE guidance.
Refereed by:	GPs with diabetes interest, Diabetes Nurse Specialists, Consultant Diabetologists, CCG Diabetes Leads & Patients'.
Approval by:	Mersey Cluster Diabetes Network (incl. Halton, Warrington & St Helens Diabetes Network), Pan Mersey APC, St Helens & Knowsley Teaching Hospitals, Royal Liverpool & Broadgreen University Hospitals, University Hospital Aintree, Warrington & Halton Hospitals.
Target population:	All staff & students involved in the clinical management of people with diabetes in Pan Mersey.
For information:	Pan Mersey Acute Trusts & CCG Diabetes Leads
Training needs:	All of those using the document are offered specific (specialist) training relating to use of the document – please contact Dr Hardy's secretary on 01744-646497.
Superseded	North Mersey District Diabetes Guidelines, 2012-14,v 17.

Introduction

The aim of these recommendations is to provide brief guidance for non-experts on common topics encountered by those caring for people with diabetes.

A tension exists between ease of reference and discussion of the evidence base for a recommendation. Professionals delivering care to people with diabetes should read these recommendations in conjunction with current NICE guidance. For detailed discussions of the evidence underpinning diabetes management in the UK, see:

NICE guidance – see www.nice.org.uk

Important Notes

- These recommendations are compliant at time of writing with NICE guidance. Evidence grades are largely based on Cochrane grading system used by NICE.

- Pragmatically, much management of Type 1 & Type 2 has been harmonised using the more up to date Type 2 guidance CG87 http://www.nice.org.uk/CG87 (the Type 1 guidance is over 5 years old and dated and to be reviewed by NICE).

- These recommendations are for guidance only. Clinicians should always use their knowledge, experience and expertise to best manage patients' individual needs and preferences.

- Drugs should be prescribed and monitored as per data sheet recommendations, or current best practice unless experience and the patient's best interests dictate otherwise. Insulin must always be administered using an insulin specific syringe or device. Insulin should be prescribed as 'units' never abbreviate to 'u' or 'iu'.

- The issue of primary prevention of vascular disease with Aspirin has received intense scrutiny and there is an emerging consensus that the benefits of aspirin for primary prevention are less than was previously thought and that the risks are greater and many commentaries have questioned the continued use of Aspirin for the prevention of vascular disease in those not known to have vascular disease. This brings into question NICE guidance on the matter which antedated some of the most recent evidence – we would advise careful consideration of the risks and benefits before using/continuing aspirin for primary prevention of vascular disease (see page 11).

Prescribing advice
6: Endocrine system
Issued: September 2012 | Revised: February 2014 | Review: September 2014
http://www.panmerseyapc.nhs.uk/formulary/documents/06-00-00_endocrine.pdf

Contents & List of Topics

Topic 1: Diagnosis of Diabetes

N.B. The diagnosis of diabetes carries important medico-legal ramifications for patients – it is important to get it right. (mM = mmol/litre).

What is NORMAL blood glucose?

NORMAL = Fasting plasma glucose (laboratory sample) (FPG) < 6.0 mM or

NORMAL = Random plasma glucose (laboratory sample) (RPG) < 7.8 mM or

NORMAL = 2 hr (120 minute) OGTT glucose (laboratory sample) < 7.8 mM

What is DIABETES - blood glucose criteria for diabetes.

DIABETES = HbA1c ≥ 48mmol/mol with OSMOTIC SYMPTOMS or

DIABETES = RPG ≥ 11.1 mM with OSMOTIC SYMPTOMS or

DIABETES = FPG ≥ 7.0 mM with OSMOTIC SYMPTOMS or

DIABETES = HbA1c ≥ 48mmol/mol x 2 without OSMOTIC SYMPTOMS or

DIABETES = RPG ≥ 11.1 mM and FPG ≥ 7.0 without OSMOTIC SYMPTOMS or

DIABETES = RPG ≥ 11.1 mM (twice) without OSMOTIC SYMPTOMS or

DIABETES = FPG ≥ 7.0 mM (twice) without OSMOTIC SYMPTOMS

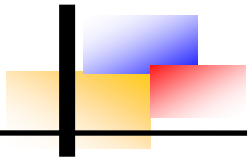
What is left?

IMPAIRED GLUCOSE REGULATION (IGR – discussed with patients as "Pre-Diabetes")
= FPG 6.0–6.9 mM (inclusive) or 2 hr post-glucose of 7.8–11.0 mM (+FPG < 7.0) on OGTT or HbA1c 42-47mmol/mol.

Notes / Further Action

- Blood glucose strips / meters are not adequate for the diagnosis of diabetes & diagnostic blood glucose thresholds for capillary blood glucose are different.
- HbA1c may be unreliable in certain circumstances e.g. haemolysis.
- If you do two HbA1c tests to establish a diagnosis of diabetes (i.e. in someone without osmotic symptoms and one is ≥ 48 and the other is <48, then they do NOT have diabetes.
- OSMOTIC SYMPTOMS typically include: thirst, polyuria, polydipsia (usually accompanied by weight loss).
- For diagnosis of GESTATIONAL diabetes – see Topic 11.
- Glucose criteria have been re-confirmed by WHO in 2006 & are those used by NICE, 2009 & HbA1c criteria proposed by WHO and ratified for England 2011.

Topic 2: Impaired Glucose Regulation (IGR) (Pre-Diabetes)



Definition

See Topic 1 for more details.

Impaired fasting glucose (IFG) = FPG 6.0 – 6.9 mM (inclusive) and Impaired glucose tolerance (IGT) = RPG 7.8 – 11.0 mM (inclusive) (with FPG < 7.0 mM.) or HbA1c 42-47mmol/mol are to be known as **IMPAIRED GLUCOSE REGULATION** (IGR) or **"Borderline Diabetes"** in discussions with patients.

Aims of Management

1. To prevent diabetes & (preferably) restore normal glucose tolerance.
2. To reduce the increased cardiovascular risk associated with IGR.
3. To detect diabetes (should it occur) early.

Management of IFG & IGT

- Regular exercise prevents or delays the onset of diabetes in high risk patients (Level A). Aim for 20-30 or more minutes of daily exercise sufficient to cause breathlessness & sweating (can be taken in 10min blocks).

- Modest weight loss prevents or delays the onset (by 3.6 yr) of diabetes in high risk patients (Level A). Aim for sustained 5-10% weight loss. See NICE Obesity Guideline for discussion of weight management http://www.nice.org.uk/CG43

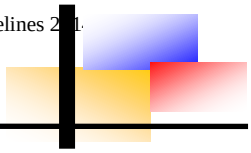
- Metformin prevents or delays the onset of diabetes in high risk patients, but it is not as effective as lifestyle measures and has been deemed not cost-effective (Level A).

- Cardiovascular risk factor modification is important (Level A), particularly as there is little evidence that exercise and weight loss reduce CV disease in this context. Consider: smoking cessation, measures to achieve BP < 140/80 & LDL-cholesterol < 2.0 mM where 10-yr CVD risk > 20% (using UKPDS risk engine).

- There is level IV evidence for screening for diabetes every 1-2 years. Nevertheless, like the American Diabetes Association, DUK & others, we recommend it in high risk patients- those with: BMI > 30 (or waist circumference > target), strong family history of diabetes, high risk ethnic groups, those who have delivered a baby of > 9 lb, hypertensive patients, PCOS patients, those with vascular disease, and if signs of insulin resistance (e.g. acanthosis nigricans) are present.

- The National Screening Committee (NSC) recommends targeted screening for diabetes in the UK – see DH guidance.

Topic 3: Monitoring Blood Glucose Control



Methods

1. Self monitoring of capillary blood glucose (SMBG) or "BMs".
2. Glycated haemoglobin (HbA1c).

Self Monitored Plasma Glucose (SMPG) - "Home Readings"

- See Mersey Network Guidance (www.northmerseydiabetes.nhs.uk/), 2011.
- All major authorities recommend frequent (≥ 4x daily) SMBG in Type 1 diabetes to monitor for extreme hyper- or hypoglycaemia. Aim pre-prandial 4-7 mM and post-prandial < 8.5 mM (Level E [Level A for intensive regimens]).
- SMBG in Type 2 diabetes. NICE (CG87 & CG66) recommends that Type 2 patients are only offered SMBG as part of self-management education. SMBG education must include: purpose of monitoring, interpretation of results and acting on results. NICE says SMBG should be available in T2DM (Level E):
  - To those on insulin treatment
  - To those on OHAs to inform about hypoglycaemia
  - To assess changes in BG resulting from medications & lifestyle changes
  - To monitor changes during intercurrent illness
  - To ensure safety during activities, including driving

- Type 1 patients should be supplied with and instructed in use of urine ketone testing strips (some T1DM patients now use blood ketone monitoring) . Following NHS Ombudsmen's report of premature death of a Halton patient, there is a case for a similar approach for Type 2 patients if there is diagnostic uncertainty or previous DKA. Which patients to issue with strips is a judgement for the assessing clinician.

- We recommend that any Type 1 patient and relevant (see above) Type 2 patients with a SMBG reading ≥16mM, check for ketones and know what to do if ketones present. GPs should seek specialist advice if unsure what to do.

Glycated Haemoglobin (HbA1c)

- HbA1c is the current gold standard for monitoring blood glucose control. It reflects control over 2-3 months & should be performed 2-6 monthly (depending on adequacy and stability of results). HbA1c underestimates glycaemia in conditions of reduced red cell survival (e.g. haemolysis) – consider other assessments.

- We recommend individualised HbA1c targets agreed with patients as suggested by NICE:

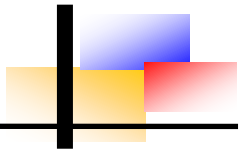
  Target HbA1c is informed by the balance between benefits of tight blood sugar control versus the risks. For newly diagnosed T2DM HbA1c target < 48 mmol/mol, but with more intensive treatment (as hypoglycaemia risk increases), target rises to <58 mmol/mol (see NICE guidance & White A *et al*. Making sense of outcomes in the ACCORD Trial. Pract Diab Int 2011;28:102-3).

Prescribing advice

BLOOD GLUCOSE TESTING STRIPS

The Pan Mersey Area Prescribing Committee recommends the prescribing of Blood Glucose Testing Strips in accordance with the supplied guidance.
http://www.panmerseyapc.nhs.uk/recommendations/documents/PS1365.pdf

Topic 4: Annual Review in people with Diabetes



What to do

- General Diabetes review and formal assessment of need for re-education (Level D, but national (DH) requirement from 2006)
- Surveillance for complications (Level C):
    - Accredited digital retinopathy screening
    - Accredited foot screening
    - Blood pressure assessment (see Topic 6 for targets)
    - Cardiovascular risk assessment (see Topics 6-8)
- Blood & urine tests:
    - HbA1c (see Topic 3) (Level D)
    - Serum creatinine & eGFR (Level C)
    - Non-fasting lipids (see Topic 7) (Level C)
    - Urine for Albumin:creatinine ratio (ACR) (Topic 12) (Level C)
    - Tests related to therapy (e.g. LFTs)

Actions

As well as general diabetes and lifestyle review and appropriate re-education, consider:

Weight Management we discuss weight management with all overweight patients and consider pharmacological support (such as Orlistat) in anyone with BMI > 28. See NICE Obesity guidance (http://www.nice.org.uk/CG43) for detailed discussion of weight reducing measures and consider local Weight Management Programmes.

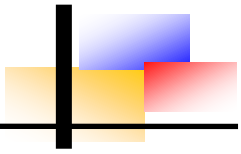
HbA1c: review with patient lifestyle changes and medications (including insulin). Refer to hospital specialist team if recurrent, problematic or severe hypoglycaemia, or for insulin initiation if expertise and resources for starting insulin and ongoing support (including robust governance arrangements) are not assured in primary care, or if sub-optimal control despite primary care interventions, or if patient prefers.

eGFR: if reduced, review medications – are they implicated or cautioned or contraindicated? Consider referral to Specialist Diabetes (Nephropathy) Clinic if eGFR < 45 (CKD 3B) or deteriorating at > 2 ml/min/year in presence of raised ACR.

Urine ACR: consider referral for specialist assessment (& likely discharge) if ACR raised. Refer all patients with ACR ≥ 30 (overt nephropathy), where discharge will be dictated by complexity of treatment & co-morbidities & risk of CKD progression).

Non-fasting lipids: see Topic 6.
Hypertension: see Topic 7.
Microalbuminuria or Nephropathy: see Topic 12
Retinopathy or visual problems: consider referral to ophthalmologist if recommended by accredited optometrist- (Liverpool & North Mersey Retinal Screening Programmes refer directly to ophthalmologist).

Topic 5: Diabetes and Driving



****N.B. People with diabetes must inform their motor insurance company**

DVLA guidance about diabetes and driving is reviewed every 6 months. We therefore strongly recommend that you consult the website for the latest advice.

http://www.dft.gov.uk/dvla/medical.aspx

Essentially:

Insulin-treated patients must inform the DVLA, must monitor blood glucose and take appropriate action, must recognise warning symptoms of hypoglycaemia and must meet required visual standards. In addition, they must not have any other conditions (e.g. neuropathy leading to loss of joint position sense) that would compromise safe driving – see website.

Temporary Insulin Treatment

E.g. gestational diabetes & post-myocardial infarction. Patients may retain licence but should stop driving if experiencing disabling hypoglycaemia. Notify DVLA again if treatment continues for more than 3 months – see website.

Diet & Tablets

Patients will be able to retain "Till 70 licence" unless develop relevant disabilities e.g. diabetic eye problems affecting visual acuity or visual field or if insulin required. In the absence of complications, diet and tablet-treated patients need not routinely inform the DVLA – see website.

GLP-1 Analogs & Gliptins combined with Sulphonylurea

– see website.

Group 2 Entitlement (LGV & PCV) & Other special licences

– see website.

Diabetic Complications, (including Hypoglycaemia)

– see website.

Topic 6: Diagnosis and Management of Hypertension in Diabetes

Diagnosis

- If clinic BP ≥ 180/110, consider starting antihypertensive drug treatment immediately. If papilloedema or retinal haemorrhage [accelerated] or labile/ postural BP↓ (20mmHg SBP fall), or headache, palpitations, pallor, sweating [phaeochromocytoma], refer same day for specialist care.

- If clinic BP ≥ 140/90 (but <180/110), offer ambulatory blood pressure monitoring (ABPM) to confirm diagnosis of hypertension (use home (HBPM) if patient declines or is intolerant of ABPM).

- Consider specialist referral if features suggest secondary hypertension.

- Use ABPM or HBPM for monitoring patients with 'white coat BP↑'.

- See http://guidance.nice.org.uk/CG127/NICEGuidance/pdf/English

Treatment

Offer lifestyle interventions to all patients

Offer drug treatment if:

Stage 1 BP↑ (*ABPM ≥135/85) - and Age < 80yr
Stage 2 BP↑ (*ABPM ≥ 150/95) - all patients

Drug Choices

Diabetes is specifically excluded from the treatment algorithm outlined in CG127 and so in the absence of contraindications renin-angiotensin-aldosterone system blockade with a long-acting generic ACE-inhibitor remains first-line treatment in diabetes (generic ARB if ACE-intolerant).

Target Clinic BP < 140/80

Thereafter, treatment with a long-acting generic calcium channel blocker and/or a thiazide-like diuretic may be added.

Start with a long-acting generic calcium channel blocker or ACE-inhibitor + thiazide-like diuretic in people of African-Caribbean descent or aged over 55 years.

Specialist referral is appropriate for poor BP control despite 3 drugs in maximum dose.

Topic 7: Diagnosis and Management of Dyslipidaemia in Diabetes

Targets

Lipid treatment reduces cardiovascular events (Level A). NICE 2008/9 http://www.nice.org.uk/nicemedia/live/11983/40803/40803.pdf targets:

Total Cholesterol or	**< 4.0 mM**
LDL-Cholesterol (preferred measure & PRIORITY) and	**< 2.0 mM**
Non-fasting Triglycerides (lower priority than LDL)	**< 4.5 mM**

Secondary Prevention

In patients with IHD or CVD or PAD, with lifestyle measures, we recommend:

- Refer to **Specialist Lipid Clinic** if SEVERE primary or mixed hypercholesterolaemia – patient (& family) likely to need metabolic & genetic screening.

Otherwise:

- Start SIMVASTATIN 40 mg nocte & check lipids in 6 wk**,** **if LDL > 2,**

NICE CG67 (lipid modification guidelines, May 2008) recommends increasing to simvastatin 80 mg if LDL < 2 or total cholesterol < 4mmol/L is not achieved, however in May 2010 the MHRA issued a safety warning of increased risk of myopathy with simvastatin 80 mg and in June 2011 the FDA also highlighted safety concerns. Therefore, we do not currently recommend new routine initiations of simvastatin 80 mg. We would typically use a more powerful statin, such as Atorvastatin to achieve target LDL < 2.0 or total cholesterol < 4.0.

Primary Prevention

In those aged over 40 yr (unless very low CV risk) & those aged < 40 years if CV risk is high (including consideration of nephropathy and microalbuminuria), using UKPDS risk engine, in combination with lifestyle measures, we recommend:

- Start SIMVASTATIN 40 mg nocte (routine titration not recommended).

  Important note: use lower dose SIMVASTATIN (i.e. 20 mg o.d.) if combined with amlodipine, diltiazem or verapamil because of increased risk of myopathy (refer to BNF for full list of interactions).

Triglycerides

- Consider Fenofibrate if fasting Trigs >4.5 (2.3-4.5 in high risk patients) after 2^{o} causes managed, because of pancreatitis risk (but don't add fibrate to statin+ezetimibe & note ACCORD study failed to demonstrate cardiovascular advantage from statin+fibrate when compared with statin alone)

- Do not use Niacin-like drugs or Omega-3 fish oils, except under specialist advice.

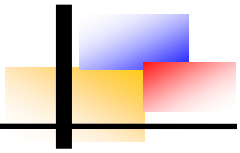
Prescribing advice

Lipid modification

NICE BITES July 2014: No 65

The Pan Mersey Area Prescribing Committee endorses UKMI North West 'NICE Bites' summary of prescribing recommendations from NICE Clinical Guideline 181 Lipid Modification 2014.
http://www.medicinesresources.nhs.uk/GetDocument.aspx?pageId=789829

Topic 8: Aspirin & Antiplatelet Therapy in Diabetes



Secondary Prevention of Vascular Disease

Use of antiplatelet therapy in people with known pre-existing vascular disease is associated with improved outcomes (whether or not they have diabetes). In the absence of contraindications, the following patients should receive **ASPIRIN 75 mg o.d**.:

Diabetes + myocardial infarction
Diabetes + angina
Diabetes + stroke (cerebral infarct) or TIA (Clopidogrel 75 mg o.d. preferred for stroke)
Diabetes + peripheral arterial disease (Clopidogrel 75 mg o.d. preferred for PAD)

Combination with other anti-thrombotic agents may also be indicated e.g. with Clopidogrel or other antiplatelet agents in ACS & AMI.

Primary Prevention of Vascular Disease

The Anti Thrombotic Trialists Collaboration (ATT-C) metanalysis (May 2009) examined 6 primary prevention trials, including 95 000 individuals with low average cardiovascular risk and 16 2° prevention trials with 17 000 individuals who had high cardiovascular risk showed that primary prevention of vascular events with Aspirin is of uncertain value, whereas, the risk of major episodes of haemorrhage may increase. The ATT-C updated their recommendations for Aspirin in primary prevention after considering the results from POPADAD, JPAD, AAA trials. They concluded that the benefits of Aspirin appeared to outweigh its risks when used in 2°, but not primary prevention.

De Berardis conducted a 2nd metanalysis of 6 studies with 10 117 participants, which suggested that the benefit of Aspirin in primary prevention and major cardiovascular events or death in people with diabetes may be lower than in other high risk populations. Evidence demonstrating that low dose Aspirin is beneficial was lacking in this analysis and the benefits were not found to exceed the risk for major bleeding, particularly in patients at low cardiovascular risk and in older patients at high risk of bleeding. Subsequently the American Diabetes Association revised its guidelines and backed off its recommendations for the use of Aspirin in the primary prevention of vascular disease.

In July 2010 the NHS Regional Drug & Therapeutic Centre concluded: 'currently, the balance of evidence does not support the widespread use of Aspirin in the primary prevention of cardiovascular disease, including in patients with hypertension or diabetes'; 'patients currently receiving Aspirin for primary prevention of cardiovascular disease should have their medication reviewed'.

Thus, there was mounting evidence and authoritative opinion that routine use of Aspirin in the primary prevention of vascular disease in diabetes was unproven and undesirable. What about patients with diabetes at high risk of vascular disease? Further analysis from the ATTC work and a study by Hernandez-Diaz and data from De Berardis have shown that as vascular risk increases (and the benefits of Aspirin intuitively increase), so bleeding risk also increases-thus even in higher risk primary prevention groups it is unclear whether the risks outweigh the benefits.

Against this backdrop came several papers suggesting possible reduced risk of colon and breast cancer in patients in their mid 40s taking Aspirin. Does this new evidence tip the balance back in favour of using Aspirin in primary prevention? 'No' says a BMJ analysis and commentary.

In conclusion, although there is compelling evidence for the use of Aspirin in the secondary prevention of vascular disease, evidence for the benefit of Aspirin in the primary prevention of vascular disease in people with diabetes, including sub groups of people with diabetes at high risk of vascular events, is lacking and at present it is unclear whether the benefits of Aspirin in this regard outweigh the increase risk of haemorrhage.

Topic 9: Insulins and Oral hypoglycaemic Agents in Type 1 Diabetes

We typically use one of two insulin regimens in Type 1 diabetes: basal bolus treatment (Level A) or a twice-daily fixed insulin mixture (Level D). Basal bolus regimens (4 injections per day) offer greater lifestyle flexibility for some people. Continuous Subcutaneous Insulin Infusion **("pumps")** may be suitable for some type 1 patients (NICE Technology appraisal No. 151) and is offered at local hospitals.

Insulin initiation is typically undertaken by a hospital team – intensive post-insulin-start support for patients is a critical element of insulin initiation. If this cannot be assured in primary care, referral to the hospital team is advised.

Safer insulin guidance recommends prescribing insulin by brand (i.e. non-generic) names to avoid confusion; delivery the device should also be specified. Remember do not use abbreviations 'u' or 'iu'.

B.D. Mixture

We typically use an analog mix (e.g. Humalog Mix 25), given 15 minutes before breakfast and 15 minutes before evening meal.

Analog mixes may produce less hypoglycaemia and are more convenient for patients because they can be given shortly before the meal; human insulin (e.g. Humulin M3) is less expensive.

Basal Bolus Regimen

We typically use a short-acting analog (e.g. Apidra 15 minutes before breakfast, lunch & evening meal, together with a long-acting insulin analog (e.g. Lantus) at bedtime. NPH insulin (e.g. Humulin I) is less expensive than Lantus & Levemir but may cause more nocturnal hypoglycaemia. Human insulin (e.g. Humulin S) is less expensive than fast-acting analogs, but must be given 20-40 minutes before the meal and may increase nocturnal hypoglycaemia. Tresiba is considered too expensive for routine use (there may be exceptional circumstances where it is appropriate).

Insulin + Oral Hypoglycaemic Agents

In the absence of contraindications, we consider addition of METFORMIN 500-1000mg t.d.s. to insulin in T1DM if body mass index (BMI) > 28 (Level A for T1DM – one small study).

Insulin in Pregnancy & Preconception

See Topic 11.

Insulin Dose Adjustment in Adults

Patients are taught to self-adjust. Increments and decrements must be individualised.

Prescribing advice

INSULIN DEGLUDEC 100 units/ml solution for subcutaneous injection (Tresiba®▼)

The Pan Mersey Area Prescribing Committee does not recommend the use of insulin DEGLUDEC 100 units/ml (Tresiba®▼) in the management of type 1 or type 2 diabetes.
http://www.panmerseyapc.nhs.uk/recommendations/documents/PS25.pdf

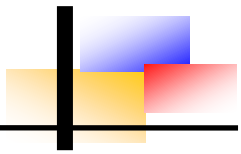
Insulin DEGLUDEC 200 units/ml solution for subcutaneous injection (Tresiba®▼)

The Pan Mersey Area Prescribing Committee recommends the restricted use of insulin DEGLUDEC 200 units/ml (Tresiba®▼) in the management of type 1 or type 2 diabetes only for patients who would otherwise require high volume insulin doses, following specialist initiation.
http://www.panmerseyapc.nhs.uk/recommendations/documents/PS26.pdf

INSULIN DEGLUDEC 100units/ml + LIRAGLUTIDE 3.6mg/ml solution for injection (Xultophy®▼)

The Pan Mersey Area Prescribing Committee does not currently recommend the prescribing of INSULIN DEGLUDEC 100units/ml + LIRAGLUTIDE 3.6mg/ml solution for injection (Xultophy®▼) for the treatment of type 2 diabetes.
http://www.panmerseyapc.nhs.uk/recommendations/documents/PS105.pdf

Topic 10: Insulins, Oral hypoglycaemic Agents (OHAs) or GLP-1 Analogs in Type 2 Diabetes



When starting Metformin up-titrate the dose over several weeks; NICE says try Glucophage SR if patient intolerant of standard release metformin.

Second-line OHA treatment is typically a sulphonylurea, e.g. Gliclazide (but Pioglitazone, a gliptin (e.g. Sitagliptin) or an SGLT2 inhibitor (e.g. Dapagliflozin) are alternatives).

In those inadequately controlled on 2 OHAs, consider insulin, triple OHA therapy or GLP-1 analog therapy, as dictated by safety, clinical need and patient preference.

Triple OHA therapy typically involves adding either Pioglitazone or a gliptin to metformin+sulphonylurea. Gliptins rarely cause weight gain or problematic hypoglycaemia and typically improve HbA1c by about 8 mmol/mol. Different gliptins have different licensed indications – see BNF or datasheets for details and latest safety issues.

Important Notes (1) Pioglitazone appears to be associated with an increased risk of bladder cancer which should be taken into consideration when choosing this drug. It should not be used in un-investigated macroscopic haematuria and should be used with care in those at increased risk of bladder cancer. Patients should be monitored at 3-6 months and regularly thereafter (see EMA guidance, July 2011). (2) Gliptins may be associated with increased pancreatitis risk you must warn about pancreatitis risk, relevant symptoms and appropriate action. (3) SGLT2 inhibitors are very new and are associated with increased risk of urinary and genital infections.

Insulin + Oral Hypoglycaemic Agents

Insulin/OHA combination therapy is the initial treatment of choice for most Type 2 patients inadequately controlled on maximal OHA treatment (unless HbA1c > 75 mmol/mol [see below]).

Insulin is added to MF & SU (Pioglitazone may be combined with insulin, but specialist initiation is strongly recommended). NPH insulin (e.g. Humulin I) is recommended 1st line by NICE or more costly Lantus or Levemir for those thought to require twice daily NPH. Insulin Detemir may be associated with less weight gain – the evidence isn't particularly strong.

When O.D. Insulin + OHA is Insufficient

Patients inadequately controlled on Insulin/OHA combination therapy (or in whom HbA1c on maximal oral therapy is ≥ 75mmol/mol) usually get either a once daily basal insulin (e.g. Lantus) + a rapid acting analog (e.g. Apidra) 15 min before their main meal (preferred) or b.d analog Mix (e.g. Humalog Mix 25), given 15 min before breakfast and evening meal. In the absence of contraindications, continue Metformin if BMI > 28.

GLP-1 Analogs

GLP analogs (e.g. Liraglutide) combined with OHAs are useful in some (BMI >30-35) Type 2 patients – see NICE. Insulin + GLP agonist in Type 2 is also licensed for certain combinations – see individual datasheets. Quadruple therapy is not recommended. See NICE e.g. technology appraisal of Liraglutide (http://www.nice.org.uk/nicemedia/live/11895/50663/50663.pdf.

Prescribing advice

GLIPTINS

GLIPTINS (Dipeptidylpeptidase-4 [DPP-4] inhibitors)
The Pan Mersey Area Prescribing Committee recommends the prescribing of DPP-4 inhibitors in accordance with NICE CG 87 – The Management of Type 2 Diabetes.
http://www.panmerseyapc.nhs.uk/recommendations/documents/PS88.pdf

ALOGLIPTIN with METFORMIN tablets (Vipdomet®▼)
The Pan Mersey Area Prescribing Committee does not recommend the routine prescribing of ORAL COMBINATION PRODUCTS that are available as the separate constituents.
http://www.panmerseyapc.nhs.uk/recommendations/documents/PS1366.pdf

LINGALIPTIN with METFORMIN tablets (Jentadueto®▼)
The Pan Mersey Area Prescribing Committee does not recommend the routine prescribing of ORAL COMBINATION PRODUCTS that are available as the separate constituents.
http://www.panmerseyapc.nhs.uk/recommendations/documents/PS1366.pdf

SGLT2 inhibitors

CANAGLIFLOZIN film-coated tablets (Invokana®▼)
The Pan Mersey Area Prescribing Committee does not currently recommend the prescribing of CANAGLIFLOZIN film-coated tablets (Invokana®▼) for the treatment of Type 2 diabetes mellitus.
http://www.panmerseyapc.nhs.uk/recommendations/documents/PS38.pdf

CANAGLIFLOZIN with METFORMIN tablets (Vokanamet®▼)
The Pan Mersey Area Prescribing Committee does not recommend the routine prescribing of ORAL COMBINATION PRODUCTS that are available as the separate constituents
http://www.panmerseyapc.nhs.uk/recommendations/documents/PS1366.pdf

DAPAGLIFLOZIN film coated tablets (Forxiga®▼) as monotherapy
The Pan Mersey Area Prescribing Committee does not recommend the prescribing of DAPAGLIFLOZIN film coated tablets (Forxiga®▼) as monotherapy for the treatment of type 2 diabetes mellitus.
http://www.panmerseyapc.nhs.uk/recommendations/documents/PS28.pdf

DAPAGLIFLOZIN film coated tablets (Forxiga®▼) as combination therapy
The Pan Mersey Area Prescribing Committee recommends the prescribing of DAPAGLIFLOZIN film coated tablets (Forxiga®▼) as add-on combination therapy for the treatment of type 2 diabetes mellitus in accordance with NICE TA288.
http://www.panmerseyapc.nhs.uk/recommendations/documents/PS1391.pdf

DAPAGLIFLOZIN with METFORMIN tablets (Xigduo®▼)
The Pan Mersey Area Prescribing Committee does not recommend the routine prescribing of ORAL COMBINATION PRODUCTS that are available as the separate constituents
http://www.panmerseyapc.nhs.uk/recommendations/documents/PS1366.pdf

GLP-1 agonitst

DULAGLUTIDE subcutaneous injection (Trulicity®▼)
The Pan Mersey Area Prescribing Committee does not currently recommend the prescribing of DULAGLUTIDE subcutaneous injection (Trulicity®▼) for type 2 diabetes.
http://www.panmerseyapc.nhs.uk/recommendations/documents/PS115.pdf

EXENATIDE solution for injection (Byetta®▼) in combination with insulin
The Pan Mersey Area Prescribing Committee recommends the prescribing of EXENATIDE solution for injection (Byetta®▼), a GLP-1 agonist, in combination with insulin in the management of type 2 diabetes mellitus.
http://www.panmerseyapc.nhs.uk/recommendations/documents/PS1398.pdf

Licensed combinations of GLP-1 agonists and insulin
Issued: September 2013 | Review: September 2015
http://www.panmerseyapc.nhs.uk/guidelines/documents/G1.pdf

GLP-1 based therapies used to treat diabetes
Issued: September 2013 | Review: September 2015
http://www.panmerseyapc.nhs.uk/safety/documents/S4.pdf

LIRAGLUTIDE solution for injection (Victoza®▼) in combination with insulin
The Pan Mersey Area Prescribing Committee recommends the prescribing of LIRAGLUTIDE solution for injection (Victoza®▼), a GLP-1 agonist, in combination with insulin in the management of type 2 diabetes mellitus.
http://www.panmerseyapc.nhs.uk/recommendations/documents/PS1399.pdf

LIRAGLUTIDE 3.6mg/ml + INSULIN DEGLUDEC 100units/ml solution for injection (Xultophy®▼)
The Pan Mersey Area Prescribing Committee does not currently recommend the prescribing of INSULIN DEGLUDEC 100units/ml + LIRAGLUTIDE 3.6mg/ml solution for injection (Xultophy®▼) for the treatment of type 2 diabetes.
http://www.panmerseyapc.nhs.uk/recommendations/documents/PS105.pdf

LIXISENATIDE injection (Lyxumia®▼)
The Pan Mersey Area Prescribing Committee recommends the prescribing of LIXISENATIDE injection (Lyxumia®▼) for the treatment of adults with type 2 diabetes mellitus ONLY WHEN BOTH EXENATIDE AND LIRAGLUTIDE ARE UNSUITABLE OR NOT TOLERATED and in accordance with the recommendations in NICE Clinical Guideline 87 and NICE TA203
http://www.panmerseyapc.nhs.uk/recommendations/documents/PS32.pdf

LIXISENATIDE solution for injection (Lyxumia®▼) in combination with insulin
The Pan Mersey Area Prescribing Committee recommends the prescribing of LIXISENATIDE solution for injection (Lyxumia®▼) in combination with insulin for the management of type 2 diabetes mellitus following specialist initiation or recommendation ONLY WHERE BOTH EXENATIDE AND LIRAGLUTIDE ARE UNSUITABLE, NOT TOLERATED OR PRESCRIBING WOULD BE OUTSIDE OF THEIR PRODUCT LICENCES.
http://www.panmerseyapc.nhs.uk/recommendations/documents/PS33.pdf

Topic 11: Contraception, Conception and Pregnancy

Contraception

Most modern forms of contraception are typically acceptable in diabetes; some gestagens carry increased venous thromboembolic risk – combined oral contraceptive pills using lowest practicable dose of oestrogen and lower risk gestagens are preferable.

Conception

Diabetes is associated with substantially increased risks to mother and baby, including greatly increased risk of congenital malformations. Near-normal glycaemic control at or near conception is likely to be necessary to reduce these increased risks.

Women with diabetes contemplating pregnancy should be referred to the specialist team for pre-conception management.

Pregnancy & Labour

People with pre-existing diabetes and gestational diabetes should usually be seen by the specialist team, as early in pregnancy as possible. Typically, pregnancy and labour are jointly managed by diabetes specialists and obstetricians. Note: Metformin or Glibenclamide may be used in some patients (specialist use only).

Gestational Diabetes

Is difficult to diagnose (there are numerous different criteria). WHO guidelines for diagnosis of diabetes in pregnancy are:

Fasting	≥ 7.0 mM
Post-prandial (e.g. 2 hr OGTT)	≥ 7.8 mM

Targets for Glycaemic Control

Target HbA1c for pre-conception and pregnancy is ≤ 43 mmol/mol. Targets for SBGM set by patient and diabetes specialist. Typically, pre-meal BMs 4-6 mM and 1-hr post-prandial BMs <7.8 mM.

Folic Acid

Current national guidelines recommend FOLIC ACID 5mg daily for women with diabetes from 3 months pre-conception to 12 weeks gestation.

Topic 12: Diabetic Microalbuminuria and Nephropathy

Untreated, diabetic proteinuria is associated with high risk of progression to renal failure and very high risk of cardiovascular morbidity and premature mortality. Level A evidence supports interventions to prevent this morbidity and premature mortality.

Albumin to creatinine ratio (ACR) on 'first pass' early morning MSSU sample sent to the hospital laboratory is the method of choice for detecting and quantifying proteinuria (Level C). If 1 ACR is raised, repeat twice more within 3-4 months (Level C).

Definitions

NORMAL = ACR < 2.5 mg/mmol in men
NORMAL = ACR < 3.5 mg/mmol in women

MICROALBUMINURIA = **2** x ACRs 2.5 – 30 in men or
MICROALBUMINURIA = **2** x ACRs 3.5 – 30 in women

NEPHROPATHY = **2** x ACR > 30

Management

(RAAS = renin-angiotensin-aldosterone system blockade e.g. ACE- or ARB)

In the absence of contraindications, there are 6 key (individualised) interventions:

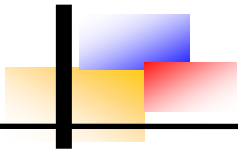
1. BP control to < 140/80 mmHg (usually requires multiple drugs) (see Topic 6)
2. RAAS blockade: Generic ACE-inhibitor (if ACE-intolerant, use ARB).
3. Statin therapy (see Topic 7): LDL-C < 2.0 mM.
4. Aspirin 75 mg o.d therapy if known vascular disease
5. Good glycaemic control, typically HbA1c < 48-58 mmol/mol (see Topics 9&10)
6. Smoking cessation

N.B. RAAS blockade should be used even if the BP is 'normal'.
Statins should be used even if the cholesterol is 'normal'.
Patients with reduced eGFR often need additional measures:

- we recommend referral to Hospital Diabetes Team

- patients likely to need complex intervention are typically shared with a nephrologist (we have pre-defined arrangements with local nephrologists and we will sort referral for 'shared care').

Topic 13: Diabetes & Endoscopy or Radiology



Diabetic patients needing endoscopic or radiological investigations may have to fast, modify their diet or receive intravenous contrast media.

For information see NHS Diabetes 2011, Management of Diabetes in Adults undergoing Surgery and Elective Procedures, Appendix 9, P62.

Summary of Common Situations and Actions for diabetes medications

	MF alone	**MF+SU or MF + TZD or MF + Insulin or MF +gliptin**	**SU or TZD or gliptin or combination**	**Insulin[4] or Exenatide or Liraglutide**
All	Pt. must monitor BMs closely seek help if problems			
IV Contrast?	Stop MF	Stop MF Continue others	Continue	Continue
Bowel Prep.?	Continue meds	Continue meds Use "Build Up" or other substitute for CHO as required.	Continue meds Use "Build Up" or other substitute for CHO as required.	Continue meds Use "Build Up" or other substitute for CHO as required.
Overnight fast?	No problem	Hypo risk Use "Lucozade" or other substitute for CHO as required.	Hypo risk Use "Lucozade" or other substitute for CHO as required.	Hypo risk Use "Lucozade" or other substitute for CHO as required.

Notes

1. MF=Metformin, SU=sulphonylurea, TZD=thiazolidenedione, BM=self monitored capillary blood glucose, Hypo=hypoglycaemic episode, CHO=carbohydrate.
2. Metformin should be stopped 48hr before intravenous contrast and not restarted until post-procedure serum creatinine confirmed normal.
3. Emergency endoscopies etc should be performed with patient on GKI (see relevant inpatient guidelines) regardless of T1DM or T2DM.
4. May need dose adjustment – if in doubt phone DNS for advice.

Topic 14: Management of Diabetic Neuropathies

There are many different forms of neuropathy in diabetes only a few are discussed.

Chronic Sensorimotor Neuropathy

Common: usually symmetrical numbness, skin changes and variable motor weakness in feet; predisposes to foot ulceration. No specific treatment. Aim for good glycaemic control & education re footcare (Community Foot Screening Programme) together with appropriate footwear to try to prevent foot ulceration.

Diabetic Painful Neuropathy (DPN)

After diagnosis of neuropathic pain & together with management of underlying condition (see http://www.nice.org.uk/nicemedia/live/13566/64189/64189.pdf):

First Line

Offer a choice of amitriptyline (unlicenced), gabapentin (licenced) or nortriptyline (unlicenced) initially. If initial treatment is not effective or not tolerated offer another one of these three agents instead.

Second Line

If initial treatment is not effective or not tolerated or is contraindicated with all 3 of these agents, consider switching to duloxetine (licenced) or pregabalin (licenced).

Consider tramadol only if acute rescue therapy is needed while the person waits for specialist appointment.

Consider capsaicin cream (0.075% Asxain) for people with localised neuropathic pain who wish to avoid or who cannot tolerate oral treatments.

Third Line

Consider referring the patient to a specialist pain service or condition-specific service at any stage, including initial presentation and at the regular clinical reviews, if:

- They have severe pain, or
- Pain significantly limits their daily activities and participation, or
- Their underlying health condition has deteriorated

Autonomic Diabetic Neuropathy

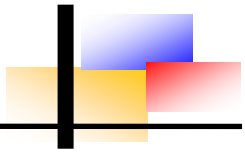
Postural hypotension, recurrent vomiting, recurrent severe diarrhoea, urinary retention, unexplained bladder emptying and gustatory sweating may result from diabetic autonomic neuropathy, typically in longstanding diabetes. If suspected, referral to the Hospital Specialist Diabetes Team for assessment and management is recommended.

Prescribing advice

Neuropathic pain: pharmacological management in non-specialist settings
Issued: September 2012 | Review: September 2014
http://www.panmerseyapc.nhs.uk/guidelines/documents/G1378.pdf

Supplementary sheet: recommended dose titrations and dose reductions in renal impairment for gabapentin and pregabalin
Issued: September 2012 | Review: September 2014
http://www.panmerseyapc.nhs.uk/guidelines/documents/G1378_supp.pdf

Topic 15: Management of Hypoglycaemia



Hypoglycaemia typically manifests as hunger, sweating, tremulousness, headache (and/or a host of other symptoms), with or without confusion and reduced conscious level in association with a blood sugar, typically < 4.0 mM. Some patients suffer seizures during hypoglycaemia and some develop (reversible) hemiparesis.

Oral Treatment

Glucose (e.g. 4 dextrosol or half a glass of lucozade) is the best treatment for hypo, but a glass (150 ml) of fresh orange juice, sugary (3 sugars) tea is ok.

A rapidly absorbable sugary solution is available (GLUCOGEL). This may be used in semiconscious patients (who can still protect airway) if parenteral treatment and emergency help is not available (not in unconscious patients).

If short-acting carbohydrate (as above) is used then it should be followed up by more complex carbohydrate (such as a sandwich) to prevent further hypoglycaemia.

Strive for a BM ≥ 8.0 mM before discharging the patient from clinical supervision.

If Patient can't take Carbohydrate by mouth

If the patient is unable to take oral carbohydrate then:

1 mg of glucagon may be given IM or IV while awaiting an ambulance (999). Glucagon may cause headache and vomiting (especially in young – consider 0.5 mg in teenagers).

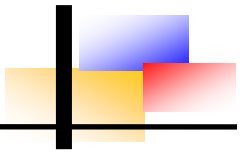
Sulphonylurea-induced hypoglycaemia may require prolonged treatment and supervision – refer for hospital admission.

Subsequent Management

Severe hypoglycaemia is often recurrent – after one episode people are particularly susceptible to further episodes over the next few days or more. After an episode of severe hypoglycaemia, patients should be advised to run their sugars higher (say 8-15 mM) for a week or so and should avoid driving or other situations where hypo would put them or others at risk

→ referral to the Hospital Specialist Diabetes Team is recommended.

Topic 16: Patients who we advise should be seen by Hospital Adult Specialist Diabetes Services



Precise criteria vary slightly within the Pan Mersey Region.

Diabetes & pregnancy (T1DM or T2DM)
Diabetes in pregnancy (GDM)
Diabetes & planning pregnancy
Young people (18-25 yr) with diabetes
Newly diagnosed T1DM
People with Diabetes wanting DAFNE-like education
Patients admitted to hospital & found to have problematic diabetes
Patients with severe, unexplained or recurrent hypo
Patients with hypo unawareness
Patients wishing to be considered for Insulin Pump Therapy
Patients where differentiation between T1DM & T2DM is in doubt
Maturity onset diabetes of the Young (MODY)
Problematic painful neuropathy
Autonomic neuropathy
Neuropathic or neuroischaemic foot ulceration
Diabetes + ACR > 30
Diabetes + eGFR < 45 (CKD Stage 3B)
Persistent poorly controlled diabetes despite basic treatment
Microalbuminuria: (i.e. ACR > 2.5 males 3.5 females)
Complex CVS patients with diabetes
New or suspected Charcot
Diabetes & sight-threatening retinopathy
Complex patients under consideration for Pioglitazone treatment
Patients for consideration for GLP Analog treatment