**Cardiovascular Risk Factor Management (Primary Prevention)**

**Aim(s) and objective(s)**

Morbidity and mortality from cardiovascular disease (coronary artery disease, cerebrovascular disease and peripheral vascular disease) is significantly higher among people with diabetes compared to those without diabetes.

Life expectancy of people diagnosed with Type 2 Diabetes at age 40 is reduced by approximately eight years relative to those without diabetes and most of this excess mortality is from cardiovascular disease. South Asian people with diabetes are at particularly high risk of cardiovascular disease.

Appropriate management of cardiovascular risk factors reduces cardiovascular events.

This guideline will focus on the **PRIMARY PREVENTION** of cardiovascular disease in people with diabetes using:

1. Antiplatelet therapy
2. Lipid Lowering therapy
3. Blood Pressure (BP) therapy

The vast majority of available evidence for the management of cardiovascular risk in diabetes comes from trials involving people with Type 2 Diabetes. In practice we tend to apply the same guidelines & targets for cardiovascular risk factor management to people with Type 1 Diabetes.

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**User group**

All health care professionals involved in the care of people with diabetes, in particular, hospital physicians, diabetes specialist nurses, general practitioners and practice nurses.

Particular care must be taken when prescribing for the elderly, pregnant women and women of childbearing age and patients with renal disease.

**THESE GUIDELINES ARE FOR THE PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE AND DO NOT APPLY TO THOSE WHO ALREADY HAVE DOCUMENTED CARDIOVASCULAR DISEASE.**

**THESE GUIDELINES ARE INTENDED FOR USE AMONG ADULT PATIENTS ONLY.**

**MANY OF THE DRUGS USED FOR TREATING HYPERTENSION & HYPERLIPIDAEMIA ARE POTENTIALLY TERATOGENIC AND SHOULD NOT BE USED IN WOMEN OF CHILDBEARING AGE WITHOUT APPROPRIATE COUNSELLING AND IDEALLY ROBUST CONTRACEPTION.**

This guideline is not intended to serve as a protocol or standard of care. Rather, each patient must be assessed individually and the guideline applied taking into account the clinical context. This guideline may be subject to change as scientific knowledge and technology advances and as patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should it be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same result. Ultimately a judgement must be made by the healthcare professional(s) responsible for a particular clinical procedure or treatment plan following discussion with the patient, covering the diagnostic and treatment options available. It is advised that any significant departure from the guideline should be documented in the patient’s medical record at the time the decision is taken.
Guideline

**LIFESTYLE MODIFICATION:**
All patients should be advised on lifestyle measures including diet, weight loss (where appropriate), smoking cessation and regular exercise to reduce their cardiovascular risk.

**GLYCAEMIC CONTROL:**
Epidemiological studies demonstrate a clear association between poor glycaemic control and increased cardiovascular risk. More controversial however is whether or not tightening glycaemic control lowers that risk or whether the increased cardiovascular disease seen in patients with higher HbA1c levels is simply indicative of the ‘severity of diabetes’.

Glycaemic control is important for improving symptoms and reducing microvascular disease complications.

For recommendations on management of glycaemia please see separate guidelines on the management of glycaemic control in Type 1/Type 2 Diabetes.

**ANTI-PLATELET THERAPY:**
Low-dose aspirin is not currently recommended for routine primary prevention of cardiovascular disease in people with diabetes. The benefits of daily aspirin for the primary prevention of CVD in patients with diabetes and CVD risk factors (but without known CVD) is uncertain. The small potential benefit of treatment with low-dose aspirin on cardiovascular outcomes, however, is offset by the increased risk of gastrointestinal bleeding.

Low-dose aspirin may be considered for patients who are deemed to be at particularly high risk of cardiovascular disease e.g. patients with multiple additional vascular risk factors, those with microalbuminuria/ diabetic nephropathy and patients who are of South Asian origin.

It should be noted that low-dose aspirin is not licensed for primary prevention in diabetes and the risk of gastrointestinal haemorrhage should be weighed against any potential cardiovascular risk reduction and discussed with the patient prior to embarking on therapy.

**BLOOD PRESSURE CONTROL:**
Hypertension is more common in patients with Type 2 Diabetes than in those without diabetes and is a major risk factor for cardiovascular disease.

Hypertension should be aggressively managed in patients with diabetes hence blood pressure targets are lower than those for hypertensive patients without diabetes. Many patients require several agents in order to achieve adequate blood pressure control.

Blood pressure control is also important to prevent and to delay the progression of microvascular disease, in particular retinopathy and nephropathy. Patients with documented microalbuminuria/nephropathy should be treated with an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) IRRESPECTIVE OF BLOOD PRESSURE and tight blood pressure control is particularly important in this group of patients (see separate guideline on Diabetes and Kidneys). Patients on ACEIs/ ARBs should be advised to stop these medications during intercurrent illness, particularly if they have a dehydrating illness, such as gastroenteritis.

**Recommended Targets:**
Systolic Blood Pressure target is <= 130 mmHg*
Diastolic Blood Pressure target is <= 80 mmHg*
Drug therapy (summarised in flow chart):**

People with diabetes requiring antihypertensive therapy should normally be commenced on an ACE Inhibitor (ACEI) or Angiotensin receptor blocker (ARB) first line. (Consider treatment with thiazide diuretic as first line therapy for those of African-Caribbean origin). The dose should be titrated up to the maximum dose (if tolerated) with monitoring of urea and electrolytes (U&Es). A generic ACEI is recommended but if side effects develop e.g. cough then an ARB should be considered.***

Second, a thiazide diuretic or calcium channel blocker (CCB) should be considered (with CCB titrated to the maximum tolerated dose).

Third, a CCB or thiazide should be considered.

If blood pressure is not controlled on three agents after following the above recommendation then consider adding a β blocker, α blocker or aldosterone antagonist.

β blockers, α blockers and aldosterone antagonists should not be used in the first line management of hypertension in people with diabetes unless there is a specific indication (e.g. β blockers in patients with ischaemic heart disease).

Consider specialist referral if:
- blood pressure is not adequately controlled on 3-4 agents
- the patient has features of hypertension due to secondary cause e.g. Cushing’s, Acromegaly
- the patient is <35 years of age
- there are other concerns e.g. severe hypertension, deteriorating renal function, proteinuria

*** ACEI/ARB should not be used where pregnancy is a possibility due to potential teratogenicity. They should only be used in women of child bearing age with extreme caution, appropriate counselling and ideally robust contraception. CCB should be used as first-line therapy in this group.

Monitoring:
Measure blood pressure at least annually in patients without previously diagnosed hypertension or renal disease.
Repeat blood pressure in those diagnosed with hypertension within:
- 1 month if BP > 150/90 mmHg
- 2 months if BP > 130/80 mmHg
- 6 months if BP <130/80 mmHg
and review for potential side effects of treatment.

LIPID LOWERING THERAPY:
Dyslipidaemia (high total and LDL cholesterol, low HDL cholesterol and raised triglycerides) is common in patients with Type 2 Diabetes.

Lipid lowering with statins is proven to reduce cardiovascular disease in people with diabetes. The relationship between hypercholesterolaemia and cardiovascular risk appears to be linear with no obvious cut-off above or below which cardiovascular risk levels out. The absolute risk reduction with statin therapy is, however, higher in patients with higher baseline cholesterol concentrations i.e. patients at higher risk.

Lipid lowering therapy is recommended with simvastatin 40mg or atorvastatin 10mg daily for all** patients with diabetes (without known cardiovascular disease) above the age of 40, irrespective of baseline cholesterol, to reduce cardiovascular risk. **MHRA advice recommends a maximum dose of Simvastatin 20mg with CCBs Amlodipine, Diltiazem, Verapamil and with Amiodarone.
Recommendations:

For patients over 40 years old with diabetes prescribe Simvastatin 40mg at night irrespective of baseline lipid levels. If this is not tolerated or contraindicated (e.g. drug interaction) consider substituting with Atorvastatin 10mg at night.

For patients with particularly high cardiovascular risk (e.g. microalbuminuria, multiple risk factors, South Asian ethnicity) aim for targets of Total Cholesterol < 4mmol/L & LDL < 2mmol/L. If these are not achieved on Simvastatin 40mg then change to Atorvastatin 40-80mg at night or Rosuvastatin 10-20mg at night.

Consider statin therapy for ‘high risk’ patients under the age of 40

**Statins are contraindicated in pregnancy and should be used with extreme caution including patient counselling in women of child-bearing age.**

Statin intolerance:

Hepatic dysfunction. Clinical studies of statins have demonstrated a 0.5 to 3.0 % occurrence of persistent elevations in aminotransferases in patients receiving statins. This has primarily occurred during the first three months of therapy and is dose-dependent.

Rhabdomyolysis is a rare complication of statin use and is probably somewhere in the order of 1 case for every 20,000 patient years of exposure. Reported deaths due to statin induced rhabdomyolysis were recently put at 0.15 per million prescriptions issued. Risk is increased where patients have other risk factors e.g. untreated hypothyroidism and concomitant fibrate use. The risk of severe statin related illness is tiny compared to, e.g., the risk of GI bleeding with aspirin use.

Myositis (muscle symptoms associated with a rise in serum creatinine kinase to >=10x upper limit of normal) occurs more commonly but the incidence was still < 0.5% of patients in the large statin trials. Patients who develop myositis or rhabdomyolysis should stop statin therapy.

Myalgia occurs more frequently (2-11% of patients in clinical trials of statins). Patients who develop myalgic symptoms (typically proximal symmetrical muscle weakness and pain within weeks to months of starting statin therapy) should have a trial period off treatment (until symptoms resolve), thereafter an alternative statin should be commenced. If symptoms persist despite switching statins and reducing the dose, the dose interval could be decreased from daily to alternate days or twice a week. The risks vs. benefits of statin therapy (or indeed any drug used for primary prevention) should be discussed with the patient as clearly these drugs will not make the patient feel better.

Triglycerides & Fibrates:

The evidence for the use of fibrates in primary prevention is less clear. If you are considering treatment on the basis of triglyceride levels it is important to remember the following:

1. Triglycerides should be measured on a fasting sample.
2. Poor glycaemic control (and in particular severe insulin deficiency) is likely to lead to elevated triglyceride levels and this usually be addressed prior to considering fibrate therapy.
3. Untreated hypothyroidism can lead to significant dyslipidaemia and so TSH should be measured and hypothyroidism treated if present.
4. Treating hypercholesterolaemia with a statin is also likely to improve triglyceride levels especially in patients with significantly elevated cholesterol levels.
This guideline does not recommend the routine use of fibrates for the primary prevention of cardiovascular disease in patients with diabetes. If there is concern over elevated triglyceride levels referral to a specialist diabetes or lipid clinic should be considered. Bezafibrate M/R 400mg daily is the drug of choice in the NHS Lanarkshire Joint Formulary but should be used under specialist advice only.

**Ezetimibe:**
Ezetimibe - lowers cholesterol on its own, or in combination with a statin, however there is no convincing evidence that it improves clinical end points, so routine use of Ezetimibe in the primary prevention of CVD risk in those with diabetes is not recommended. The use of Ezetimibe is reserved for treatment of familial hypercholesterolaemia under specialist advice only.

**Monitoring**
We recommend that lipids (total cholesterol, LDL, HDL, triglyceride) levels be checked annually as part of a diabetes ‘annual review’.

Liver function tests should be checked prior to initiation of statin therapy however routine monitoring of liver function in patients receiving statin therapy is not necessary and LFTs should only be repeated if there is a clinical indication. Patients who have an alanine aminotransferase (ALT) rise to more than three times the upper limit of normal that is confirmed on a second occasion should reduce their statin dose.

*** FIBRATES AND STATINS SHOULD NOT BE PRESCRIBED TO PREGNANT WOMEN OR WHERE PREGNANCY IS A POSSIBILITY.

See NHS Lanarkshire Joint Formulary recommendations per drug class for the Primary Prevention of Cardiovascular Disease
Figure 1: Management of Hypertension in the Primary Prevention of Cardiovascular Disease in People with Diabetes

**Blood Pressure Management**

**Target <130/80mmHg**

- Monitor BP annually if <130/80mmHg and no renal disease
- If BP >130/80mmHg, confirm on further 2 occasions within 1-2 months
- If confirmed hypertension and BP treated to <130/80, monitor every 6 months

**Trial lifestyle measures alone for 3 months**

- Start ACE Inhibitor and titrate dose
- Start thiazide diuretic if Afro-Caribbean
- Start Calcium Channel Blocker in women contemplating pregnancy and titrate dose

**Add a 2nd agent - thiazide diuretic or calcium channel blocker**

**Add a 3rd agent – calcium channel blocker or thiazide diuretic**

**Add a 4th agent – α blocker or β blocker**

**Consider specialist referral for consideration of aldosterone antagonist or potassium sparing diuretic**

Continue lifestyle intervention
References

Further Reading
These guidelines broadly reflect the SIGN guideline for the management of diabetes (SIGN 116).
*Blood pressure targets are taken from the SIGN guideline.
The flow chart for the scheme for the management of hypertension is adapted from the NICE guideline on the management of hypertension in diabetes. SIGN broadly concurs with this scheme but is less prescriptive in the order in which antihypertensives are used.
NICE blood pressure targets differ in that they set a target of \( \leq 140/80 \) mmHg for people with diabetes but \( \leq 130/80 \) mmHg for those who also have documented microalbuminuria or cerebrovascular disease.

**Diabetes MCN endorsement**
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