Contents

Type 2 diabetes: The management of type 2 diabetes

Type 2 diabetes mellitus is a progressive long-term medical condition that is predominantly managed by the person with the diabetes and/or their carer as part of their daily life. Accordingly, understanding of diabetes, informed choice of management opportunities, and the acquisition of relevant skills for successful self-management play an important role in achieving optimal outcomes. Delivery of these needs is not always assured by conventional clinical consultations. Structured programmes have been designed not only to improve people s knowledge and skills, but also to help motivate and sustain people with diabetes in taking control of their condition and in delivering effective self-management.

Discussion

The GDG noted that the last review of this area by a HTA on behalf of NICE in 2003 looked at the evidence for structured education. Little robust evidence of

the effectiveness of any particular educational approach for people with Type 2 diabetes was found. One conclusion was that further research was required, but meanwhile that educational programmes with a theoretical basis demonstrated improved outcomes, and that group education was a more effective use of resources and may have additional benefits.

Offer structured education

Offer structured education to every person and/or their carer at and around the time of diagnosis, with annual reinforcement and review. Inform people and their carers that structured education is an integral part of diabetes care. '

Evidence Statement CG66ES1

Please refer to the Technology Assessment Report The clinical effectiveness of diabetes education models for Type 2 diabetes: a systematic review commissioned by the NHS R&D Health Technology Assessment (HTA) programme on behalf of the NCC-CC. Available at www.ncchta.org/project/1550.asp

Fibrates have a long and controversial history as lipid-lowering agents, beginning with clofibrate over 30 years ago and being implicated in the problems which led to withdrawal of cerivastatin in the 1990s. However, bezafibrate, fenofibrate and ciprofibrate have shown considerable staying power in the market. Statins have, however, eclipsed fibrates as primary cholesterol-lowering agents, so the issues surrounding fibrates relate to specific lipid abnormalities. In clinical practice these mostly concern hypertriglyceridaemia, itself strongly associated with low HDL-C levels, this problem being particularly common in people with Type 2 diabetes (more so than raised LDL-C levels). The clinical question then relates to whether and when a fibrate should be initiated before statin therapy, and the circumstances under which a fibrate should be added to, or substituted for, statin therapy

Discussion

While the evidence was not as strong as for the statins, there was convincing evidence of the effectiveness of fibrates in CV protection in people with Type 2 diabetes. Some of the trials (e.g. FIELD) in which this evidence was found included people with TG levels down to the upper end of the normal range (~1.8 mmol/l). However, while the price of fibrates was considerably above that of generic statins, the more effective fibrates as judged by TG lowering were about half the price of proprietary statins when both are used at standard doses. Hypertriglyceridaemia is a complex condition with both a genetic basis and often being secondary to other medical conditions, including poor blood glucose control. The GDG recognised it was not writing a guideline on management of

hypertriglyceridaemia in people with Type 2 diabetes, but because of the interaction with blood glucose control and other medical conditions often associated with Type 2 diabetes (including renal impairment and liver disease), it could not avoid some general guidance in the area. In drawing up the recommendations the GDG was also cognisant of the need to be aware of:

- the likely combination with statin therapy (given its recommendations on statins) and the higher rate of side effects of combined usage
- the more immediate risks of pancreatitis with higher levels of TGs
- the difficulty of assessing LDL-C levels when TG levels were above 4.5 mmol/l. A useful pragmatic compromise was felt to be to base recommendations around cut-off levels of 2.3 and 4.5 mmol/l. There is evidence of differences between fibrates: gemfibrozil had greater interactions with other drugs commonly used in diabetes care; bezafibrate was cheaper and less effective in TG lowering and with a poorer CV evidence base than fenofibrate; and ciprofibrate was more poorly investigated. Therefore recommendations were based around fenofibrate, though with a role for bezafibrate where CV risk was less pronounced, and ciprofibrate as an alternative. Further information on fibrate statin combinations might become available when the ACCORD trial reports.35

When to perform full fasting lipid profile

If there is a history of elevated serum triglycerides, perform a full fasting lipid profile (including HDL cholesterol and triglyceride estimations) when assessing cardiovascular risk annually. ’

Cholesterol lowering remained difficult, and indeed controversial, until the late 1980s when statins became available. Subsequently these drugs became the mainstay of lipid-lowering therapy, supported eventually by CV outcome studies. As discussed above, people with Type 2 diabetes are at high CV risk, and most of their morbidity and increased mortality comes from coronary, cerebral, and peripheral arterial disease. In earlier NICE technology appraisals (TAs) and the prior Type 2 diabetes guideline, statins were recommended for all people with extant CVD or at high risk thereof, states which include most people with Type 2 diabetes.283 Clinical questions which arise include whether more potent and more expensive statins should ever be used (and if so when), the use of statins in younger people with Type 2 diabetes, whether any people should not be routinely given statins, and the use of alternatives such as fibrates (addressed in the following fibrate section) and ezetimibe addressed by a 2007 NICE TA.2

Discussion

The GDG were cognisant of the previous NICE statin appraisal, the prior Type 2 diabetes guidelines, the ezetimibe appraisal, the deliberations of the NICE guidelines group on management of CVD, and the health economic analysis. The evidence of effectiveness and safety of generic statins, and in particular simvastatin seemed clear, and at current prices probably cost saving in the population with Type 2 diabetes over the age of 40 years (irrespective of experienceof CVD). There may be individuals in this group at lower CV risk (discussed in section 13), butthese people would be uncommon and easily identified by the absence of CV risk factors (see13.1.6). In others statin therapy should usually be with generic simvastatin at standard dosage(40 mg) in line with the prior TA283 and the Heart Protection Study. The group recognised that some people below the age of 40 years were also at high risk (10 year risk >20%, or 20 year risk >40%). It was considered that they would have to be identified by conventional risk factors; presence of features of the metabolic syndrome, strong family history, ethnic group, and evidence of microvascular damage such as nephropathy. Such people would then be treated with a statin, particularly as their 10-year risk horizon came to include 40 yearsof age or greater. However, the contraindication of the use of statins in pregnancy was felt to begreat enough to deserve special mention, for any woman of childbearing potential. The health economic analysis suggested titration to simvastatin 80 mg was highly cost-effective in those whose lipid levels were not controlled to target levels of 4.0/2.0 mmol/l (T-/LDL-C) irrespective of presence or absence of diagnosed CVD. In those with CVD the health economic analysis suggested that uptitration from simvastatin 80 mg to a more efficacious statin (modelled as atorvastatin 80 mg daily) was cost-effective if the titration targets were not met on the simvastatin.

Therapy for person 40 years old and over

For a person who is 40 years old or over: initiate therapy with generic simvastatin (to 40 mg) or a statin of similar efficacy and cost unless the cardiovascular risk from non-hyperglycaemia-related factors is low (see 1.9.1) if the cardiovascular risk from non-hyperglycaemia-related factors is low, assess cardiovascular risk using the UKPDS risk engine (see 1.9.2) and initiate simvastatin therapy (to 40 mg), or a statin of similar efficacy and cost, if the cardiovascular risk exceeds 20% over 10 years. ’

Abnormalities of blood lipid profiles, including serum HDL-C and TGs, are recognised CV riskfactors, and are particularly likely to be abnormal in people with Type 2 diabetes. Nicotinic acid preparations are one approach to improving lipid profiles. Nicotinic acid administration isassociated with side effects due to vasodilatation, and derivatives (acipimox) and modified-release preparations have been made available to try and reduce the problem. The clinical question is then what role nicotinic acid derivatives might have in the management of

Type 2 diabetes.

Discussion

This group of drugs was not considered in the previous guideline (2002).414 The limitednumber of studies presented suggested that nicotinic acid can have some advantageous effect on serum HDL-C and lipids, but also that it has some negative effects on blood glucose control. In the absence of outcome trials in people with Type 2 diabetes, and given also the problems of using the current preparations (notably flushing despite prophylactic aspirin, dose titration and use of modified-release preparations), no general recommendation could be given for use of nicotinic acid. The group were aware of some possible special indications in people with extreme hypertriglyceridaemia, but felt this to be outside the remit of the current guideline.

Do not use nicotinic acid preparations routinely

Do not use nicotinic acid preparations and derivatives routinely for people with type 2 diabetes. They may have a role in a few people who are intolerant of other therapies and have more extreme disorders of blood lipid metabolism, when managed by those with specialist expertise in this area. ’

Evidence Statement CG66ES195

Overall nicotinic acid was found to show reduction in LDL, TGs and the TC/HDL ratio and increases in HDL, compared with placebo in all three studies with more significant changes for doses of 1,500 mg/day and greater. Level 1+

[1]

[2]

[3]

Evidence Statement CG66ES196

Nicotinic acid showed some glycaemic effects compared with placebo, one study identified that HbA1c remained stable with nicotinic acid but had a significant decrease with placebo, this study included a down titration of nicotinic acid if HbA1c exceeded 10%, this occurred in N=10 of the nicotinic acid group and N=8 of the placebo group.304 Two studies identified an increase in HbA1cwith doses of 1,500 mg/d, compared with placebo for both immediate-release and extended-release formulations.305,306 Level 1+

[4]

[5]

[6]

Evidence Statement CG66ES197

Increases in uric acid were identified in two of the studies, for one this was from 339 to 386 mol/l and was significant compared with placebo, p<0.001.304 The second study noted that N=2 participants had very high uric acid levels of 684 and 761 mol/l.306The third (extended-release) study found no significant differences in uric acid levels.305 Flushing was considered a minor complaint in one study, numbers not reported.306 Two thirds of those taking the extended-release nicotinic acid formulation reported flushing at some point during the trial, approximately 10% of those taking placebo reported it.305 Level 1+

[5]

[6]

Evidence Statement CG66ES198

One study considered nicotinic acid 1,500 mg/day compared with pravastatin 40 mg/day, followed by a combination therapy phase of nicotinic acid 1,000 mg/day with pravastatin 20 mg/day. This study included both diabetic and non-diabetic participants (N=11, Type 2 diabetes).307 This study considered the results for lipid profiles for the combined diabetic and non-diabetic participants. The glycaemic effect results were considered separately for diabetic and non-diabetic participants. Lipid profiles Nicotinic acid was not found to be more effective than pravastatin as the later showed significant reductions in LDL and TC levels compared with nicotinic acid. Combination therapy showed significant decreases in LDL, TC and TG levels compared with nicotinic acid and significant increases in HDL and decreases in TG levels compared with pravastatin. Level 1+

[7]

Evidence Statement CG66ES199

Diabetic participants: nicotinic acid monotherapy showed an increase in HbA1c by approximately8% (p=0.03), pravastatin showed no change in HbA1c level and the increase seen with combination therapy was non-significant. Nicotinic acid monotherapy increased FPG by approximately 26% (p=0.02), there were no changes with pravastatin or combination therapy. Non-diabetic participants: nicotinic acid monotherapy showed an increase in HbA1c by approximately 4% (p=0.02), combination therapy showed an increase of approximately 6% (p<0.01), pravastatin showed no change. None of the treatments showed changes in FPG. Level 1+

[7]

Evidence Statement CG66ES200

All of the participants in the nicotinic acid group complained of flushing, this generally lasted from 10 to 15 minutes and was ameliorated with aspirin. Nine participants (21%) withdrew from this study with significant flushing or nausea with nicotinic acid, one participant withdrew with nausea from the pravastatin group. Level 1+

[7]

The concept of beneficial and harmful dietary fats has come to the fore in recent years. Some evidence does exist for the use of omega 3 fish oils in certain circumstances such as post-MI. The clinical question then was what role these oils might have in the management of people with Type 2 diabetes.

Discussion

From the evidence available fish oils as a homogeneous therapeutic concept is problematic, as the evidence included showed a variation in the fish oil dosage used. Clinical experience confirmed that large total doses of oils used to get an adequate dose of omega 3 fish oils in some preparations can cause adverse effects. From the evidence available omega 3 fish oil preparations could help lower TG levels, but overall showed minimal improvement in lipid profiles in people who had not had a MI. The GDG agreed there were financial consequences in prescribing omega 3 supplements when the evidence showed no clear benefit. It was recognised that the recommendations made must be understood as only applying for omega 3 fish oil supplementation, and not to recommendations on sources of dietary fats.

Do not prescribe fish oil preparations for primary prevention of cardiovascular disease

Do not prescribe fish oil preparations for the primary prevention of cardiovascular disease in people with type 2 diabetes. This recommendation does not apply to people with hypertriglyceridaemia receiving advice from a healthcare professional with special expertise in blood lipid management. ’

Evidence Statement CG66ES201

The table above details the evidence from the RCTs comparing omega 3 and placebo, or corn oil or fish oil. All studies (Cochrane review and the five RCTs)

found that treatment with omega 3 significantly reduced TGs compared to placebo. Level 1+

[???]

[8]

[9]

[10]

[11]

Evidence Statement CG66ES202

The only other area where the Cochrane review identified significant changes was in LDL-C where omega 3 were associated with a significant increase compared with placebo. Level 1++

[???]

Evidence Statement CG66ES203

A subgroup analysis was undertaken with the hypertriglyceridaemic participants, doses of fish oil and trial duration. Hypertriglyceridaemic participants (control TGs >4 mmol/l) An increased reduction in TGs was identified in trials (N=3) with only hypertriglyceridaemic participants; 1.45 mmol/l (2.89 to 0.01, p=0.05), compared with studies with non hypertriglyceridaemic participants (N=11) 0.40 mmol/l (0.61 to 0.19, p=0.0002). Increases in LDL-C levels were significant in the hypertriglyceridaemic groups (N=2 trials), 0.6 mmol/l (0.16 to 1.04, p=0.008), but they were NS in the non-hypertriglyceridaemic groups(N=9 trials). Dose of fish oil Trials with high doses of fish oil (>2 g EPA, N=4) showed a significant increase in LDL-C 0.51 mmol/l (0.18 to 0.84, p=0.003), this was NS for lower doses (<2 g EPA, N=7). Levels of TGs in the high-dose groups decreased by 1.11 mmol/l (2.21 to 0.10, p=0.03), but in the low-dose group this was less at 0.54 mmol/l (0.69 to 0.38, p<0.00001). Trial duration In trials of longer than 2 months LDL-C levels increased by 0.33 mmol/l (0.00 to 0.65, p=0.05), the increases were NS in trials shorter than 2 months. TG levels were reduced by 0.81 mmol/l (1.21 to 0.41, p=0.00008) in the longer trials and by less than 0.36 (0.58 to 0.13, p=0.002) in the shorter ones. Level 1++

[???]

Evidence Statement CG66ES204

The study which included fish meals found that compared with the control (no fish meals, light exercise) the inclusion of a daily fish meal significantly reduced

TGs, 0.91.3 mmol/l, p=0.0001, with fish/moderate exercise reducing by 1.210.3 mmol/l and fish/light exercise by 1.220.3 mmol/l p=0.0001. The addition of exercise without the fish also showed a significant decrease in TGs 0.70.3 mmol/l, p=0.03, compared with the control.317 HDL-C (subgroups) The study which included fish meals found that high-density lipoprotein 2 cholesterol (HDL2-C) was significantly increased, 0.06 mmol/l, p=0.01 and high-density lipoprotein 3 cholesterol (HDL3-C) significantly reduced by the inclusion of fish compared with the low-fat control group, 0.05 mmol/l, p=0.01.317 Level 1+

[12]

Evidence Statement CG66ES205

Cardiovascular effects A meta-analysis found that participants who took omega 3 fatty acids had a significant reduction in diastolic BP of 1.79 mmHg (95% CI, 3.56, 0.02; p=0.05) and a non-significant reduction in systolic BP (p=0.32). There was also a non-significant reduction in heart rate (p=0.52).312 Level 1++

[13]

Evidence Statement CG66ES206

Thrombogenic factors The pooled analysis of the data of two studies, showed a significant increase in factor VII of 24.86% (95% CI, 7.17, 42.56; p=0.006).312 Level 1++

[13]

[14]

Antiplatelet therapy now has an established role in the management of people at high risk of cardiovascular (CV) events. People with Type 2 diabetes are known to have CV risk higher than matched populations after allowance for other CV risk factors, and in some studies as high as those without diabetes who have declared cardiovascular disease (CVD).273 National guidelines and the previous NICE (inherited) Type 2 diabetes guideline recommend use of aspirin in people at high CV risk.319,320 Other antiplatelet agents (clopidogrel and dipyridamole modified release (MR)) have been the subject of a NICE technology appraisal (TA) but without specific calculation for the higher CV event rate or the specific risk reduction in people with Type 2 diabetes.321 The increasing occurrence of Type 2 diabetes in younger people raises the additional question of the use of antiplatelet therapy in those who CV risk may be not be very high. The guidelines are not concerned with the use of antiplatelet therapy after acute cardiological events or cardiac interventions, or after acute cerebrovascular events. The clinical question then is whether antiplatelet medications should be used in people with Type 2 diabetes, or in which subgroups of such people, and if so which agents and in what doses.

Discussion

Little extra evidence of note on use of aspirin was available since the last review. However, there is now better understanding of the extent of the CV risk faced by people with Type 2 diabetes. The rather poor direct evidence for people with Type 2 diabetes led to difficulties in assessing the level of risk above which aspirin therapy should be advised. The GDG accepts that its view that all people at, or over, the age of 50 years should treated is somewhat arbitrary. Primary prevention below that age would be by assessment of higher CV risk (family history of premature vascular disease, abnormal lipid profile, marked abdominal adiposity). While thegroup were aware of some discussions over the dose of aspirin to be used in people withdiabetes, they were not presented with any evidence that could lead to a variation from the usual national recommendations of 75 mg.NICE guidance for dipyridamole MR related only to people with cerebrovascular events. The evidence for the use of clopidogrel was noted to relate to acute and non-acute situations. The current guideline review was not concerned with acute vascular events or interventions. The CHARISMA and MATCH trials suggested that the combination of aspirin and clopidogrel carried a significant side-effect risk of a serious nature not balanced by secure health gain, and therefore could not be generally recommended. NICE guidance for secondary prevention of vascular events in people without diabetes was that clopidogrel should not be used instead of aspirin except where intolerance or hypersensitivity to the latter was present. The specific evidence for people with diabetes, mostly sub-analyses, did not suggest that advice should be varied for people with Type 2 diabetes.

When to offer low dose aspirin to person 50 years old and over

Offer low-dose aspirin, 75 mg daily, to a person who is 50 years old or over, if blood pressure is below 145/90 mmHg ’

Evidence Statement CG66ES207

This study found that there was a significant decrease in proteinuria with aspirin (15.9%),with dipyridamole (14.8%) and with the combination of aspirin and dipyridamole (37.3%) compared with an increase in proteinuria found with placebo (1.9%), p=0.0007. Significantdecreases were also identified in the urinary protein/creatinine ratio with the three treatmentgroups compared with the placebo.There were no changes identified in BP, renal function tests and blood sugar. No adverse events(AEs) were noted during this study. Level 1+

[15]

Evidence Statement CG66ES208

This study was terminated early (3.7 years) and in the diabetic subgroup there were no significant changes identified with aspirin in incidence of major CV and cerebrovascular events. Level 1+

[@2001]

Evidence Statement CG66ES209

CAPRIE: Post hoc sub-analysisThis sub-analysis found a significantly lower incidence of CV events in diabetic patients receiving clopidogrel compared to those treated with aspirin. Furthermore, the incidence of rehospitalisation for any bleeding event was significantly lower with clopidogrel than with the aspirin group (see table 15.1). Level 1+

[16]

Evidence Statement CG66ES210

The authors acknowledged several limitations of this sub-analysis:

- compared with the original CAPRIE primary cluster endpoints this was a different endpoint (softer according to the authors)
- the study was not sufficiently powered to allow identification of specific individual endpoints
- the duration and severity of diabetes were unknown
- specific details regarding control of diabetes, such as glycosylated haemoglobin levels or glycaemic control were not collected. Level 1+

[16]

Evidence Statement CG66ES211

CHARISMA study The CHARISMA study did not find a significant benefit associated with clopidogrel plus aspirin as compared with placebo plus aspirin in reducing the incidence of the primary endpoint of MI, stroke, or death from CV causes in patients with clinically evident CVD or at high risk for such disease. Level 1++

[17]

Evidence Statement CG66ES212

The same study found a moderate, though significant, benefit associated with clopidogrel plus aspirin as compared with placebo plus aspirin in reducing the secondary composite endpoint of MI, stroke, or death from CV causes, or hospitalisation for unstable angina, transient ischemic attack or revascularisation (see table 15.2). Level 1++

[17]

Evidence Statement CG66ES213

[17]

Evidence Statement CG66ES214

A subgroup analysis suggested that in the population of patients with clinically evident CVD (symptomatic) the combination of clopidogrel plus aspirin was significantly beneficial in comparison with placebo plus aspirin with respect to the primary efficacy endpoint. (Among the 12,153 symptomatic patients, there was a marginally significant reduction in the primary endpoint with aspiring plus clopidogrel. See table 15.3.) Level 1++

[17]

Evidence Statement CG66ES215

The analysis suggested that there was a risk associated with dual antiplatelet therapy in the asymptomatic group since among the 3,284 asymptomatic patients there was a 6.6% relative increase in the rate of primary events with clopidogrel plus aspirin, compared to 5.5% with placebo (see table 15.3). Level 1++

[17]

Evidence Statement CG66ES216

Furthermore, in the subgroup of asymptomatic patients, there was a significant increase in the rate of death from all causes among the patients assigned to clopidogrel plus aspirin as compared with those assigned to placebo plus aspirin, as well as a significant increase in the rate of death from CV causes among those assigned to the combination therapy (see table 15.3). Level 1++

[17]

Evidence Statement CG66ES217

The rates of severe bleeding were higher, but not significant, among both the asymptomatic and symptomatic patients receiving the combination therapy compared to those receiving aspirin plus placebo (see table 15.3). Level 1++

[17]

Evidence Statement CG66ES218

Among asymptomatic patients, there was no significant difference in the rates of moderate bleeding between the two groups. In contrast, the rates of moderate bleeding among symptomatic patients were significantly higher in those treated with aspirin plus clopidogrel than in patients receiving aspirin plus placebo (see table 15.3). Level 1++

[17]

Evidence Statement CG66ES219

CREDO study The CREDO study found that at 12 months long-term clopidogrel and aspirin treatment significantly reduced the risk of death, MI or stroke in comparison with those treated with clopidogrel and aspirin for 4 weeks and then aspirin plus placebo for 11 months. RR reduction of 27%, 95% CI (3.9%44.4%), p=0.02. Absolute reduction 3% (p=0.02). Level 1++

[18]

Evidence Statement CG66ES220

The study also showed that the clopidogrel pre-treatment loading dose did not significantly reduce the combined risk of death, MI, or urgent target vessel revascularisation at 28 days. Level 1++

[18]

Evidence Statement CG66ES221

There was no significant difference in the risk of major bleeding between the groups, though there was a higher risk of major bleeding identified for those treated with long-term clopidogrel and aspirin compared with those taking aspirin plus placebo. Level 1++

[18]

Evidence Statement CG66ES222

MATCH study The study found that combination treatment with aspirin plus clopidogrel did not significantly reduce the primary composite CV morbidity or mortality endpoint* compared with clopidogrel plus placebo. Level 1++

[19]

Evidence Statement CG66ES223

MATCH study The study found that combination treatment with aspirin plus clopidogrel did not significantly reduce the primary composite CV morbidity or mortality endpoint* compared with clopidogrel plus placebo. Level 1++

[19]

Evidence Statement CG66ES224

The secondary endpoint analysis (ischaemic stroke and/or vascular death, all-cause stroke, non fatal events and rehospitalisation) showed no significant difference between the addition of aspirin to clopidogrel versus clopidogrel plus placebo, though rates were lower with aspirin than with placebo, added to clopidogrel. Level 1++

[19]

Evidence Statement CG66ES225

In terms of AEs, the study concluded that adding aspirin to clopidogrel resulted in significantly more bleeding complications than in the placebo and clopidogrel arm, doubling the number of events (see table 15.4). Level 1++

[19]

Evidence Statement CG66ES226

There was no significant difference in overall mortality between the two treatment groups. The most common type of haemorrhagic complication was GI bleeding. Level 1++

[19]

Evidence Statement CG66ES227

Post hoc analysis found no significant difference among the 5,197 diabetic patients included in the MATCH trial in terms of the incidence of primary endpoint. Level 1++

[19]

Kidney disease in people with Type 2 diabetes is becoming an ever larger health burden.336 This reflects a number of trends including the increasing prevalence of people with diabetes, the better cardiovascular (CV) survival with modern management, and the better management of progression of kidney damage itself. The trend to younger onset of Type 2 diabetes is also likely to see more kidney damage as these people are at lower CV risk, while in the elderly the condition is ever more complicated by comorbidities disease. Primary prevention of kidney damage from diabetes centres around the prevention of microvascular (classical diabetic nephropathy) and arterial (and thus renovascular) damage discussed in other chapters of this guideline the current section is concerned with detection and secondary prevention of kidney damage. For reasons of coherence some recommendationsoverlap with, or are reproduced from, other sections of the guideline. The clinical questions addressed here include how often and by what means to detect and confirm the possibility of diabetic renal disease, and the means of monitoring its progression. In those with detected renal disease issues arise as to the means to reduce or stop such progression, and the point at which to engage specialist renal management.

Discussion

Kidney disease in people with Type 2 diabetes is becoming an ever larger health burden.336This reflects a number of trends including the increasing prevalence of people with diabetes, the better cardiovascular (CV) survival with modern management, and the better management of progression of kidney damage itself. The trend to younger onset of Type 2 diabetes is also likely to see more kidney damage as these people are at lower CV risk, while in the elderly the condition is ever more complicated by comorbidities disease. Primary prevention of kidney damage from diabetes centres around the prevention of microvascular (classical diabetic nephropathy) and arterial (and thus renovascular) damage discussed in other chapters of this guideline the current section is concerned with detection and secondary prevention of kidney damage. For reasons of coherence some recommendations overlap with, or are reproduced from, other sections of the guideline. The clinical questions addressed here include how often and by what means to detect and confirm the possibility of diabetic renal disease, and the means of monitoring its progression. In those with detected renal disease issues arise as to the means to reduce or stop such progression, and the point at which to engage specialist renal management.

Fist pass morning urine specimen

Ask all people with or without detected nephropathy to bring in a first-pass morning urine specimen once a year. In the absence of proteinuria/urinary tract infection (UTI), send this for laboratory estimation of albumin:creatinine ratio. Request a specimen on a subsequent visit if UTI prevents analysis. '

Evidence Statement CG66ES228

One study344 reported that in the whole CKD group (diabetics and non-diabetics N=828), the MDRD equation was superior to the CG equation in terms of bias. The MDRD equation slightly underestimated the measured eGFR while the CG equation significantly overestimated the eGFR (0.5 vs 3.5 ml/min per 1.73 m2 $p<0.001$). Level 2+

[20]

Evidence Statement CG66ES229

The study344 showed that the MDRD equation was also significantly less biased than the CG in the diabetic subgroup (N=249) and in people with a measured GFR <30 ml/min per 1.73m2 (N=546) $p<0.001$ in each group. Level 2+

[20]

Evidence Statement CG66ES230

The study344 concluded that the MDRD and CG equations were significantly more biased in people with GFR >60 ml/min per 1.73 m2 (N=117). The MDRD equation underestimated the measured eGFR, while the CG equation significantly overestimated the GFR (3.5 vs 7.9 ml/min per 1.73 m2, $p<0.001$). The equations were also biased, but to a lesser extent in patients with GFR 3060 ml/min per 1.73 m2. Level 2+

[20]

Evidence Statement CG66ES231

One study345 revealed a bias for the MDRD and MCG the differences between the predicted and the measured GFR were correlated with their means (MDRD: $r=0.054$, $p<0.0001$; MCG: $r=0.27$, $p<0.001$). There was no such bias for CG.

[21]

Evidence Statement CG66ES232

In terms of test correlation, the study344 demonstrated that in the CKD population, both the MDRD (r=0.90) and CG equations (r=0.89) correlated highly with measured125 I-iothalamate GFR. Level 2+

[20]

Evidence Statement CG66ES233

One study345 showed that over the whole population the mean isotopic GFR was 56.534.9 ml/min/1.73 m2, the mean CG 61.235.6 ($p<0.01$ vs isotopic), the mean MCG. 60.029.9 ($p<0.05$ vs isotopic) and the mean MDRD, 51.024.3 ($p<0.001$ vs isotopic). The MCG was better correlated with isotopic GFR than was the CG (CG: r=0.75, MCG: r=0.83; $p<0.05$ vs CG, MDRD: r=0.82; p=0.068 vs CG). Level 2+

[21]

Evidence Statement CG66ES234

In relation to accuracy, the study344 showed that in the diabetic group, the MDRD equation was significantly more accurate (63%) than the CG equation (53%) $p<0.05$. Level 2+

[20]

Evidence Statement CG66ES235

One study345 stated that the receiver operating characteristic (ROC) curves showed that the MDRD and the MCG had a better maximal accuracy for the diagnosis of moderate (N=119; area under curve (AUC): 0.866 for CG, 0.920 for MDRD, 0.921 for MCG; both 0.891 vs CG) and severe (N=52; AUC: 0.891 for CG, 0.930 for MDRD, 0.942 for MCG; both $p<0.05$ vs CG) renal failure. Level 2+

[21]

Evidence Statement CG66ES236

The same study345 concluded that as the MCG was more accurate for high GFR, and the MDRD was more accurate for low GFR, the MCG could be used at low serum creatine values and the MDRD at high values

[21]

Evidence Statement CG66ES237

One study339 comparing the Micral-Test II with nephelometry demonstrated that the dipstick had a sensitivity of 83% and a specificity of 96%. The correlation between nephelometry and Micral Test II results was 0.81 ($p<0.0001$). Level 2+

[22]

Evidence Statement CG66ES238

The same study339 showed that when the ROC curve for the Micral-Test II as a diagnostic test for microalbuminuria was analysed, the calculated mean area under the ROC curve (SEM) was 0.910.03 (CI 95% 0.850.96) and the corresponding best cut-off value was 30.5 mg/l. Level 2+

[22]

Evidence Statement CG66ES239

One study343 comparing the Micral-Test II with UAER (in a 24-hour timed urine collection) reported a sensitivity 88% and a specificity 80%. When performance was assessed by different concentrations readings the study found that Micral-Test II strips performed reasonably well at 0.50 and 100 mg/l with a high percentage of true negatives (93%, 0 mg/l), true positives (81%, 50 mg/l and 91%, 100 mg/l), low percentages of false negatives (7%, 0 mg/l) and false positives (19%, 50 mg/l and 9%, 100 mg/l). However, at 20 mg/l Micral strips did not perform well (51% false positive). Level 2+

[23]

Evidence Statement CG66ES240

One study340 assessing the accuracy of the Micral-Test II, the UAC and the ACR in a random urine specimen found the following test correlations:

- UAER vs UAC: 0.76 $p<0.0001$
- UAER vs ACR: 0.74 $p<0.0001$
- ACR vs UAC: 0.86 $p<0.0001$ The study340 also reported that age and 24-hour creatinuria presented a negative correlation (278 patients, $r=0.19$, $p=0.002$). No correlation was observed between age and UAER ($r=0.02$, $p=0.74$), age and UAC ($r=0.07$, $p=0.22$) and age and UACR ($r=0.11$, $p=0.08$). Level 2+

[24]

Evidence Statement CG66ES241

The same study340 showed that the specificity of UAC and UACR was similar when considering the 100% sensitivity cut-off points. The sensitivity and specificity of the Micral-Test II strip for a 20 mg/l cut-off point (as indicated by manufacturer) on fresh urine samples based on ROC curve analysis (N=130) were 90 and 46% respectively. Level 2+

[24]

Evidence Statement CG66ES242

In terms of accuracy, the study340 stated that the comparison among the areas under the ROC curves for UAC, UACR and the Micral-Test II took into account the individual results, for each single patient (N=130), of the three screening methods being tested and of the reference test method (UAER).The study concluded that a similar area was observed under the UAC (0.9340.032) and UACR (0.9200.035) curves (p=0.626). The area under the curve was smaller for the Micral-Test II (0.8460.047) than for UAC (p=0.014). Level 2+

[24]

Evidence Statement CG66ES243

One study337 analysed the status of GFR (by DTPA renal scan) vis–vis other non-invasive modes of assessment of renal involvement (UAER, serum creatinine and ultrasound) in 100 Type 2 diabetes patients. Patients were divided into three subgroups depending on the duration of initial detection of Type 2 diabetes. Group A constituted patients with less than 5 years duration, group B 515 years and group C more than 15 years duration.

[25]

Evidence Statement CG66ES244

The study337 reported that most of the patients in group A and B had a large kidney with preserved corticomedullary (CM) differentiation (83.9% and 80%); only group C had a significantly higher prevalence of large kidney with loss of CM differentiation (75.9%). Level 2+

[25]

Evidence Statement CG66ES245

The study337 concluded that there was no difference between group A and B as far as the serum creatinine was concerned. High level of serum creatinine was only significantly associated with group C (44.8%). Level 2+

[25]

Evidence Statement CG66ES246

The study337 found that normoalbuminuria and microalbuminuria were significantly higher in group A (25.8% and 74.2%). Macroalbuminuria was higher in both group B and C (80% and 69%). For UAER group A had a significantly lower level compared to both B and C ($p<0.01$), however, there was no significant difference between group B and C with respect to the amount of both micro- and macroalbuminuria. Level 2+

[25]

Evidence Statement CG66ES247

The study337 showed that group A presented a significantly higher prevalence of normal and raised GFR (25.8% and 61.3%). Group B had a significantly higher prevalence of low GFR, while prevalence of very low GFR was highest in group C (37.9%). The GFR had a progressively significant decrement from group A through group B to C ($p<0.01$). Level 2+ The study337 concluded that GFR estimation was the only renal parameter which could singly provide a picture of the actual renal status of Type 2 diabetes patients at any duration irrespective of the status of albuminuria, azotaemia or renal size and morphology as their variability or progression is non-linear

[25]

Evidence Statement CG66ES248

After ranking 4,303 diabetics based on their eGFR (>90, 9060, 6030 and <30 ml/min per 1.73 m2) one study338 showed that the proportion of individuals with abnormal serum creatinine rose with progressive fall in eGFR (0%, 1%, 37% and 100% with creatinine >120 mol/l in eGFR >90, 9060, 6030 and <30 ml/min per 1.73 m2 respectively), as did the proportion with abnormal albuminuria (33%, 27%, 42% and 77% with ACR >3.5 mg/mmol). Level 2+

[26]

Evidence Statement CG66ES249

The study338 found that of the 1,296 individuals with an eGFR <60, 539 (42%) had abnormal serum creatinine, 579 (45%) had abnormal albuminuria and 798 (62%) had either abnormal serum creatinine or urine ACR. Thus, a creatinine and ACR based strategy would have missed the renal risk of 498 (38%) individuals since they had normal values of both despite having a significantly impaired eGFR <60 ml/min per 1.73 m2. Level 2+

[26]

Evidence Statement CG66ES250

The same study338 also demonstrated that the proportion missed by current markers was more marked in women (N=757) where the prevalence of those with abnormal serum creatinine, urine ACR and either were 20%, 38% and 47% respectively, compared with 72%, 54% and 83% observed in men (N=539). Level 2+

[26]

Evidence Statement CG66ES251

When the study analysed the data by ethnic origin, it was found that white people appeared to benefit the most from eGFR, with a greater prevalence of normocreatinaemic and normoalbuminuric renal insufficiency, whereas the majority of the African-Caribbean group with low eGFR had either an abnormal creatinine or ACR 39%, 42% and 59% respectively, with abnormal creatinine, ACR and either in white people (N=997); 62%, 69% and 80% respectively, in African-Caribbeans (N=84); and 44%, 54% and 69% respectively in Indo-Asians (N=210). Level 2+

[26]

Evidence Statement CG66ES252

The study did not find difference in performance when data was analysed by the type of diabetes. Level 2+

[26]

Evidence Statement CG66ES253

The study338 concluded that GFR estimates may have a place in routine diabetes clinical care, being a more sensitive marker of risk than serum creatinine or

albuminuria. eGFR also appears to eliminate the gender and ethnic bias observed with current markers and also provides an opportunity to monitor longitudinal changes.

[26]

Evidence Statement CG66ES254

Another study342 using data from 7,596 diabetics found that 27.5% (N=1,715) of the population had an eGFR <60 ml/min/1.73 m2; of these 19.4% had normoalbuminuria; 20.4% had albuminuria, the remainder not having had albuminuria determined.* The study also reported that serum creatinine was normal (120 mmol/l) in 54.7% of those with eGFR <60 ml/min/1.73 m2 and 150 mmol/l in 82.2%. Level 2+

[27]

Evidence Statement CG66ES255

This study342 found that the sensitivity of abnormal serum creatinine levels in identifying eGFR <60 ml/min/1.73 m2 is 45.3%, albuminuria is 51.2% and either an abnormal serum creatinine or albuminuria is 82.4%. Level 2+

[27]

Evidence Statement CG66ES256

The same study also reported that unidentified CKD, defined as the presence of a GFR <60 ml/min/1.73 m2 but without any evidence of an abnormal creatinine (i.e. serum creatinine 120 mmol/l) was significantly greater in females compared with males adjusting for age, type of diabetes and secondary care setting (OR 8.22, CI 6.56 to 10.29). Using albuminuria as a screening test also failed to identify CKD in females (OR 2.22, CI 1.63 to 3.03). The presence of abnormal serum creatinine and albuminuria to identify CKD continued to display a significant bias against females (OR 7.58, CI 5.44 to 10.57). Level 2+

[27]

Evidence Statement CG66ES257

The study342 concluded that current screening techniques based upon albuminuria and/or abnormal serum creatinine would fail to detect a significant number of participants with an eGFR <60 ml/min/1.73 m2. Therefore, without eGFR reporting the clinician may not be alerted to the presence of CKD and be falsely reassured that renal function is normal.

[27]

Evidence Statement CG66ES258

One study341 divided 301 Type 2 diabetes patients on the basis of their GFR (i.e., < or =60 ml/min 1.73 m2) and albuminuria status (i.e., normo <20 g/min, micro 20200 g/min, macro >200 g/min). The study found a significant correlation between a decreasing GFR with increasing levels of AER (r=-0.29, p<0.0001). Level 2+

[28]

Evidence Statement CG66ES259

The study341 reported that for the 109 patients with a GFR <60 l/min 1.73 m2 the prevalence of normo-, micro- and macroalbuminuria was 39%, 35% and 26% respectively. For the 192 patients with a GFR =60 ml/min 1.73 m2 the prevalence of normo-, micro- and macroalbuminuria was 60%, 33% and 7% respectively. Level 2+

[28]

Evidence Statement CG66ES260

When the study341 stratified the 301 patients according to their AER status regardless of their GFR, 52% had normo-, 34% had micro-, and 14% had macroalbuminuria. For the 158 normoalbuminuric patients, 27% had a corresponding GFR <60 ml/min 1.73 m2 and 73% had a GFR =60 ml/min 1.73 m2. Level 2+

[28]

Evidence Statement CG66ES261

The study also demonstrated that normoalbuminuric patients were significantly older (p<0.01) and more commonly female (p<0.01) in comparison to those with macroalbuminuria. There were no differences in the duration of diabetes, BMI, prevalence of retinopathy, history of CVD, smoking history, HbA1c levels, systolic blood pressure, diastolic blood pressure (DBP), total cholesterol, low-density lipoprotein, high-density lipoprotein and triglyceride levels among patients with a GFR <60 ml/min 1.73 m2 associated with normo-, micro-, or macroalbuminuria.

[28]

Evidence Statement CG66ES262

Overall, the study did not find significant differences in the use of any antihypertensive agent (specifically renin-angiotensin system inhibitors (RAS-inhibitors))

for patients with a GFR <60 ml/min 1.73 m2 and normo-, micro- or macroalbuminuria. Level 2+

[28]

Evidence Statement CG66ES263

The study341 calculated the prevalence of a GFR <60 ml/min 1.73 m2 and normoalbuminuria after excluding 23 of 43 patients whose normoalbuminuric status was possibly altered by the use of RAS inhibitors. After this adjustment the prevalence of a <60 ml/min 1.73 m2 and normoalbuminuria was 20 of 86 (23%). Level 2+

[28]

Diabetes eye damage is the single largest cause of blindness before old age with a progressive incidence in people with Type 2 diabetes.346 The success of laser therapy in the treatment of sight-threatening retinopathy is an accepted part of ophthalmological care and has not been assessed for this guideline. Appropriate clinical questions to be addressed are, however, how people with developing retinopathy can be selected for ophthalmological referral in time for optimal treatment, and whether preventative therapy other than good blood glucose, good blood pressure, and good blood lipid control can be useful in people with Type 2 diabetes.

Discussion

It was noted that management in this area was largely determined by practice for all people with diabetes and not just those with Type 2 diabetes. Indeed retinopathy screening programmes to be provided on a local community basis were a key early target of the National Service Framework (NSF) for diabetes, and since that time the UK National Screening Programme has published and updated a workbook on Essential elements in developing a diabetic retinopathy screening programme for the guidance of health authorities and primary care trusts in England (fourth edition, January 2007).347 These observations, and a lack of awareness amongst experts of new publications that might affect recommendations on retinopathy screening, led to the conclusion that recommendations for people with Type 2 diabetes should closely follow those for Type 1 diabetes (NICE guideline 2004),26 which themselves were largely based on generic evidence independent of type of diabetes. Accordingly the recommendations of the Type 1 diabetes guidelines, and the evidence statements underlying them were reviewed, together with the national screening document. There are no significant changes from the Type 1 diabetes recommendations.

When to arrange eye screening

Arrange or perform eye screening at or around the time of diagnosis. Arrange repeat of structured eye surveillance annually. ’

Neuropathic pain is a troublesome symptom of chronic exposure to poor blood glucose control that cannot be managed acutely by restoration of blood glucose control. It can take many forms, and is often distressing and sometimes depressing, particularly if symptoms are predominantly nocturnal and disturb sleep. People with diabetes may be reluctant to report the symptoms to those with expertise in diabetes care, because of lack of awareness that the problem is diabetes related. A number of drug and non-drug approaches to management are available, this diversity reflecting that none of them are fully effective. Clinically the issues are when to start specific drug therapy for neuropathic pain, which medications to use, and in what order to try them.

Discussion

A more holistic approach was often needed at discovery of the problem in helping people tounderstand it, where secondary psychological problems occurred, and when onward referral was needed to specialist pain teams for lack of response to conventional measures.

When to enquire re development of neuropathic symptoms

Make a formal enquiry annually about the development of neuropathic symptoms causing distress. Discuss the cause and prognosis (including possible medium-term remission) of troublesome neuropathic symptoms, if present (bearing in mind alternative diagnoses). Agree appropriate therapeutic options and review understanding at each clinical contact. ’

Gastroparesis can be one of the more devastating complications of autonomic neuropathy. While it can present as bloating, nausea and fullness on eating, severe intermittent hypoglycaemia can be a major problem for people on glucose-lowering therapy, while vomiting may be intermittent and sudden or occasionally severe and protracted. The clinical questions addressed include in whom to suspect gastroparesis might be present, what medications might help, and what other measures might be taken.

Discussion

The evidence reported had methodological limitations, notably studies of small sample sizes.The GDG agreed that there is a poor evidence base for the treatment of gastroparesis. Nevertheless they noted that the evidence reported

suggested that the prokinetic drugs, metoclopramide, domperidone, along with erythromycin, were all effective in at least some people with gastroparesis resulting from autonomic neuropathy. On consideration of the evidence it was not possible to distinguish usefully between the prokinetic drugs. The group agreed that choice of initial therapy should be based on tolerability issues, including drug interactions. It was noted that differential diagnosis can be difficult, and the diagnostic tests not secure, while serious prolonged vomiting could become a medical emergency. Accordingly referral beyond diabetes services is sometimes indicated. While the group gave priority to medication for the management of this condition, clinical experience suggested that non-pharmacological approaches including postural advice and timing of ingestion of fluids and solids could prove useful to some people.

When to consider diagnosis of gastroparesis

Consider the diagnosis of gastroparesis in an adult with erratic blood glucose control or unexplained gastric bloating or vomiting, taking into consideration possible alternative diagnoses. ’

Evidence Statement CG66ES264

One crossover study with 10 participants with diabetes and known prolonged gastric emptying were given 200 mg of IV erythromycin or IV placebo.383 Ten age and sex matched health participants were also used as a comparator group. This study used scintigraphic studies and found that for 60 and 120 minutes IV erythromycin significantly increased gastric emptying, (measured as the mean percentage simultaneously ingested food retained in the stomach, for solids), compared with placebo (215 vs 857, $p<0.0005$ and 41 vs 639, $p<0.0005$ respectively). For liquids the mean percentage retained was significantly lower for the IV erythromycin compared with placebo again at both 60 and 120 minutes (225 vs 545, $p<0.0005$ and 93 vs 324, $p<0.005$ respectively).247 IV erythromycin was also found to have increased gastric emptying for solids at 60 minutes when compared with healthy subjects in the comparator group ($p<0.05$). There were no AEs found with this study, this study had a further open-label phase with oral erythromycin, not reported here. Level 1+

[29]

Evidence Statement CG66ES265

Two studies,384,385 one of which was a crossover study,384 were identified comparing oralmetoclopramide 10 mg QID and placebo, both studies used the diary recording of symptoms and though the scales used were broadly similar they were not identical, there were no major AEs identified in either study.* One study

identified that the mean symptom scores for the 3-week treatment phase was significantly less for metoclopramide than for placebo; 26.53.7 vs 45.37.8, p<0.01. This study also found that the mean individual scores for 4/5 symptoms (fullness, pressure and bloating, nausea, vomiting, anorexia) showed that metoclopramide significantly reduced the symptoms compared with placebo (p<0.05).385 The crossover study found that symptom improvement was significantly greater for metoclopramide than placebo for nausea at weeks 1 and 3 (p<0.05). This was also found for fullness at weeks 2 and 3 (p<0.05). Changes found for other symptoms were not significantly improved for metoclopramide compared with placebo.384 Level 1+

[30]

[31]

Evidence Statement CG66ES266

One study386 considered domperidone vs placebo, this study combined a 4-week period where participants took 20 mg domperidone QID (single-blind phase) orally, followed by a 4-week period of 20 mg domperidone QID or placebo (double-blind phase). Entry into the second phase was dependent on a decrease on the baseline symptom score, those classed as responders, following completion of the single-blind phase. Single-blind phase: significant symptomatic improvement was found at the end of the singleblind phase (p<0.0001). Improvements were also noted in the health-related quality of life measured on the SF-36 scale (all domains p<0.001, except physical functioning, p<0.01). Double-blind phase: symptom severity increased with both domperidone and placebo, though they did not return to baseline levels, this increase in severity was greater for placebo compared with domperidone (p<0.05). AEs were not reported. Level 1+

[32]

Evidence Statement CG66ES267

One crossover study with 13 participants considered erythromycin 250 mg TID with metoclopramide 10 mg TID. Gastric empting was considered at 60 and 90 minutes and while significant improvements were found for both drugs there was no significant difference found between the effects betweenerythromycin and metoclopramide. The symptom score was significantly less for erythromycin; 2(05), than for metoclopramide; 3(011), p<0.05. No serious AEs were noted, though N=2 of the patients did have weakness, sedation and leg cramps with metoclopramide. Level 1+

[33]

Evidence Statement CG66ES268

One study with 95 participants considered domperidone 20 mg QID with metoclopramide 10 mg QID. Gastroparetic symptoms and tolerability were assessed, it should be noted for tolerability assessment participants were specifically asked about central nervous system (CNS) associated side effects; these have previously been identified in association with metoclopramide. Although significant reductions in symptoms were found with both domperidone and metoclopramide, there was no significant difference found between the two treatments. For tolerability, at week 2 the severity of somnolence ($p<0.001$), akathisia ($p=0.03$), anxiety ($p=0.02$) and depression ($p=0.05$) were significantly greater for metoclopramide than for domperidone ($p<0.001$-0.05). While at week 4 this was found for severity of somnolence ($p=0.03$) and reduced mental acuity ($p=0.04$). Level 1+

All people with Type 2 diabetes should be supported to:try to achieve and maintain blood glucose levels and blood pressure in the normal rangeor as close to normal as is safely possible, maintain a lipid and lipoprotein profile that reduces the risk of vascular disease. Optimal dietary behaviours can contribute to all of these. Dietary intervention should address the individual s nutritional needs, taking into account personal choices, cultural preferences and willingness to change, and to ensure that quality of life is optimised. It is usual that a registered dietician plays a key role in providing nutritional care advice within the multidisciplinary diabetes team. It is also recognised that all team members need to be knowledgeable about nutritional therapy, and give emphasis to consistent dietary and lifestyle advice.11

Discussion

The GDG noted that there was little new evidence to warrant any change to previous views in this field. The major consensus-based recommendations from the UK and USA emphasise sensible practical implementation of nutritional advice for people with Type 2 diabetes. Other relevant NICE guidance should be considered where relevant, including clinical guideline no. 43 on the assessment and management of overweight and obesity in adults and children and clinical guideline no. 48 which gives dietary and lifestyle advice post-MI. Overlap with the NICE/RCP Type 1 diabetes guideline was noted. Management otherwise will concentrate on principles of healthy eating (essentially those for optimal cardiovascular risk protection), and reduction of high levels of free carbohydrate in food that are hyperglycaemic in the presence of defective insulin secretory reserve.

Provide nutritional advice

Provide individualised and ongoing nutritional advice from a healthcare professional with specific expertise and competencies in nutrition. ’

Evidence Statement CG66ES10

Barnard et al.14 investigated the effects of a low-fat vegan diet compared with a diet based on ADA guidelines, on body weight and glycaemic control in an RCT with 99 Type 2 diabetics, followed up for 22 weeks. During the study period, 43% (21/49) of vegan participants and 26% (13/50) of ADA participants reduced their diabetic medications, mainly as a result of hypoglycaemia. Eight per cent in each group, 4/49 of the vegan group and 4/50 of the ADA group, increased their medications. The study concluded that for the whole sample, body weight was reduced in both groups by 5.8 kg in the vegan group and 4.3 kg in the ADA group, but this difference was not statistically significant (p=0.082). In those whose medication was stable this difference was significant with a 6.5 kg reduction in the vegan group, and 3.1 kg in the ADA group, p<0.001. BMI declined by 2.11.5 kg/m2 in the vegan group and by 1.51.5 kg/m2 in the ADA group (p=0.08). The waistto- hip ratio declined in the vegan group 0.020.01 but not in the ADA group (p=0.003). Level 1+

[34]

Evidence Statement CG66ES11

With respect to glycaemic control, the RCT stated that while the HbA1c decline in both groups was statistically significant from their baseline values with a decline of 0.96% (p<0.0001) in the vegan group and 0.56% (p=0.0009) in the ADA group, there was no significant difference between the groups (p=0.089). Again the results were different in those participants whose medication was unchanged. The HbA1c decline was greater in the vegan group, 1.231.38%, than in the ADA group, 0.381.11%, (p=0.01). Level 1+

[34]

Evidence Statement CG66ES12

In an observational study with 4 years of follow-up,20 the authors investigated the association between eating behaviour and long-term weight gain. Ninety-seven Type 2 diabetics were recruited at diagnosis and after initial nutrition advice were followed up for a period of 4 years. The study found that at the end of follow-up, mean body weight change in men was a gain of 1.35.4 kg, whereas in women, there was a mean body weight reduction of 1.15.0 kg. These changes were not statistically significant, (p values not given). Similarly, BMI increased in men by 0.421.76 kg/m2 and decreased in women by 0.401.89 kg/m2, (p values not given). Glycaemic outcomes were not reported. Level 2+

[35]

Evidence Statement CG66ES13

In the second observational study,19 weight loss over the 6.5-year follow-up is not reported. However, metabolic control did improve in patients over the period, with the proportion of patients with HbA1c <7% increasing from 52.4% to 64.3% in men and from 43.9 to 50.9% in women. It was not reported whether or not this was significant. Level 3

[@2006]

Evidence Statement CG66ES14

The RCT by Li et al.,13 reporting on the comparison of a soy-based meal replacement plan with an individualised diet plan, did not report on changes in blood pressure during the study. For the blood lipid control outcomes, while there were no significant differences between groups during the study for lipid parameters, there were differences within the groups when compared to baseline values. In the meal replacement group, there were decreases in total cholesterol, triglycerol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) at the end of the study, however these changes were only significant in the triglycerol group with an overall decrease from baseline of 28.00 mg/dl (p=0.038). Decreases in total cholesterol were significant at 3 (p<0.0001) and 6 (p=0.0037) months, but at 12 months with a reduction of 10.76 mg/dl from baseline, this was not significant (p=0.084). LDL decreased by 11.04 mg/dl at 3 months (p=0.024), but at 12 months the change from baseline had reduced to 6.10 mg/dl (p=0.255). HDL had decreased by 0.97 mg/dl at 12 months (p=0.345). In the individualised diet plan group, after initial decreases at 3 or 6 months, at 12 months there were increases in total cholesterol by 5.26 mg/dl (p=0.396), LDL by 8.76 mg/dl (p=0.129) and HDL by 2.26 mg/dl (p=0.012). Only in triglycerol levels was there a sustained decreased at 12 months with a reduction from baseline of 28.89 mg/dl (p=0.119). Level 1+

[36]

Evidence Statement CG66ES15

In the study by Redmon17 which compared a combined intervention (described above) with an individualised diet plan, at 1 year there were reductions in systolic and diastolic blood pressure in both groups, although this did not differ between the groups. Systolic blood pressure reduced in the combination group by 63 mmHg and by 62 mmHg in the comparison group. Diastolic blood pressure reduced in the combination group by 31 mmHg and by 62 mmHg in the comparison group. Level 1+

[37]

Evidence Statement CG66ES16

At 1 year, changes in fasting cholesterol, HDL, LDL and fasting triglycerides did not differ between groups. There were reductions from baseline values in fasting cholesterol and LDL cholesterol in both groups, with a decrease in fasting cholesterol of 68 mg/dl in the combination therapy group and 179 mg/dl in the comparison group (p=0.90). LDL decreased by 125 mg/dl in the combination therapy group and 136 mg/dl in the comparison group (p=0.89). Fasting triglycerides decreased by 4624 mg/dl in the combination group compared to an increase of 818 mg/dl in the comparison group, however this was not significant (p=0.07). Level 1+

[37]

Evidence Statement CG66ES17

At 12 weeks of follow-up, in the low-carbohydrate arm of this RCT16 there was a reduction in systolic blood pressure of 6.242.96 mmHg and a reduction of 0.392.64 mmHg in the low-fat arm, with no significant difference between the arms (p=0.147). Level 1+

[38]

Evidence Statement CG66ES18

With respect to lipid parameters, there was a greater reduction in the total cholesterol: HDL ratio in the low-carbohydrate arm, mean reduction of 0.48, than in the low-fat arm, mean reduction 0.10 (p=0.011). There were also reductions in triglycerides in both arms, 0.67 mmol/l in the low-carbohydrate arm and 0.25 in the low-fat arm, which did not approach statistical significance (p=0.223). Level 1+

[38]

Evidence Statement CG66ES19

In the RCT comparing the low-fat vegan diet with the ADA diet,14,20 there were non-significant reductions in systolic and diastolic blood pressure in both groups. In the vegan group systolic blood pressure decreased by 3.812.6 mmHg ($p<0.05$) compared with baseline and in the ADA group by 3.613.7 mmHg from baseline, with no significant difference between the groups (p=0.93). Similarly the reduction in diastolic blood pressure was greater in the vegan group, 5.18.3 mmHg ($p<0.0001$) than in the ADA group 3.38.8 mmHg ($p<0.05$) although this was not different between groups (p=0.30). Level 1+

[34]

[35]

Evidence Statement CG66ES2

An RCT comparing a soy-based meal replacement with an individualised diet based on ADA recommendations in obese Type 2 diabetics13 found that average weight reduction in the meal replacement group was greater than that in the individualised diet group. At 6 months, the meal 32 Type 2 diabetes replacement group had lost on average 5.240.60 kg, and the individualised diet group had lost an average of 2.850.67 kg (p=0.0031). At 1 year this difference was not significant with the meal replacement group losing on average 4.350.81 kg and the individualised diet group losing an average of 2.360.76 kg (p=0.0670). Level 1+

[36]

Evidence Statement CG66ES20

For the entire sample, although lipid parameters decreased significantly from baseline values, there were no significant differences between groups. Among those whose lipid controlling medications remained constant (vegan N=39/49; ADA N=41/50), total cholesterol reduced in the vegan groups by 33.521.5 mg/dl ($p<0.0001$), in the ADA group by 19.028.5 mg/dl ($p<0.0001$) and this was a significantly different between groups (p=0.01). Reductions in HDL cholesterol were not significantly different between the groups. Reductions in non-HDL cholesterol were significantly lower than baseline in the vegan groups 27.621.1 mg/dl ($p<0.0001$) and in the ADA group 16.330.1 mg/dl ($p<0.05$), but not significantly different between the groups (p=0.05). LDL cholesterol reduced in the vegan group by 22.622.0 mg/dl ($p<0.0001$) and in the ADA group by 10.723.3 mg/dl ($p<0.05$), and was significantly different between the groups (p=0.02). The total-to-HDL cholesterol ratio and triglyceride concentrations fell for both groups, but there was no difference between the groups. Level 1+ 36 Type 2 diabetes RCTs T= Comparison Comparison Blood pressure Lipid levels Li (2005)13 1 year Soy-based meal Individualised diet No changes NS differences replacement Redmon 1 year Sibutramine + low Individualised diet NS differences NS differences (2003)17 calorie diet + meal replacement Daly (2006)16 3 months Low-carbohydrate Reduced portion low- NS differences TC:HDL ratio diet fat diet significantly lower in carbohydrate arm Barnard 22 weeks Low-fat vegan diet Diet based on ADA NS differences NS differences (2006)14 guidelines Table 6.2 Summarised results for blood pressure and lipid levels

[34]

[35]

Evidence Statement CG66ES21

In the observational study investigating the effect of eating behaviours on weight,20 changes in blood pressure or lipid profiles were not reported. In the diabetes nutrition and complications trial19 changes in blood pressure were reported as the proportion of patients who had a systolic blood pressure <130 mmHg, which decreased from 28.6% at baseline to 11.9% at the end of the study. Similarly in women there was a decrease from 15.8% at baseline to 8.8% after 6.5 years. The proportion of patients with a diastolic blood pressure of <80 mmHg decreased from 26.2% to 21.4% and from 31.6% to 28.1% in men and women respectively. In this study they reported the number of patients who were adherent to the ADA diet recommendations and were able to achieve the recommended intakes of various types of fats. They found that levels of adherence to the recommendations was low with only 26.6% of patients consuming the recommended amount of saturated fatty acids (SFAs), 13.0% consuming the recommended =10% of dietary energy from polyunsaturated fats, and 38.5% consuming the recommended =60% of dietary energy from carbohydrates and monounsaturated fats. They also estimated that 46.4% of patients consumed a ratio of polyunsaturated fatty acids (PUFAs)/SFAs >0.4 and 69% consumed a ratio of monounsaturated fats (MUFAs)/SFAs >1.5. Patients who consumed MUFAs/SFAs <1.5 had a 3.64.7 times greater risk of developing diabetic complications (confidence intervals (CIs) not presented). Patients who consumed PUFAs/SFAs <0.4 were 3.48.2 times more at risk of developing diabetic complications. Level 3

[@2006]

[35]

Evidence Statement CG66ES3

The same RCT reported that similar changes were observed in the body mass index (BMI) at12 months with a reduction of 1.470.27 kg/m2 in the meal replacement group and 0.770.25 kg/m2 in the individualised diet group. Although these values were significantly different from their baseline values, none were significantly different from each other (p=0.0687).Level 1+

[36]

Evidence Statement CG66ES4

The study by Redmon17 reported on a combination intervention including sibutramine, an intermittent low-calorie diet with the use of meal replacements for 1 week every 2 months, and the use of meal replacements between the low-calorie diet weeks. The comparison group received an individualised diet plan with a 5001,000 kcal energy deficit per day. The study reported that at 1 year

of follow-up, the combination therapy group had a significantly greater weight loss of 7.31.3 kg than the standard therapy group 0.80.9 kg (p<0.001), with most weight loss occurring during the low-calorie weeks and some weight gain occurring in between the low-calorie weeks. Level 1+

[37]

Evidence Statement CG66ES5

In relation to glycaemic control, the study showed that at 1 year, HbA1c had declined from a baseline of 8.10.2% to 7.50.3% in the combination therapy group but had remained unchanged at 8.20.2% in the standard therapy group, and this difference was significant (p=0.05). After adjusting for medication changes, this difference remained significant. In an analysis of those participants whose medication had not changed, it was found that there was a significant positive linear association between change in weight at 1 year and change in HbA1c (r=0.53; p=0.006). A 5 kg decrease in weight at 1 year was associated with a 0.4%

[37]

Evidence Statement CG66ES6

With respect to glycaemic control, the RCT found that mean HbA1c levels were significantly lower in the meal replacement than in the individualised diet group, 0.490.22% (p=0.0291), for the entire study period. Plasma glucose concentrations were significantly lower in the meal replacement group than in the individualised diet group at 3 (p=0.04) and 6 (p=0.002) months, but not at 12 months (p=0.595). Level 1+

[37]

Evidence Statement CG66ES7

Studies that compared a meal replacement intervention with a reduced calorie diet The RCT by Li et al.,13 reporting on the comparison of a soy-based meal replacement plan with an individualised diet plan, did not report on changes in blood pressure during the study. For the blood lipid control outcomes, while there were no significant differences between groups during the study for lipid parameters, there were differences within the groups when compared to baseline values. In the meal replacement group, there were decreases in total cholesterol, triglycerol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) at the end of the study, however these changes were only significant in the triglycerol group with an overall decrease from baseline of 28.00 mg/dl (p=0.038). Decreases in total cholesterol were significant at 3 (p<0.0001) and 6 (p=0.0037) months,

but at 12 months with a reduction of 10.76 mg/dl from baseline, this was not significant (p=0.084). LDL decreased by 11.04 mg/dl at 3 months (p=0.024), but at 12 months the change from baseline had reduced to 6.10 mg/dl (p=0.255). HDL had decreased by 0.97 mg/dl at 12 months (p=0.345). In the individualised diet plan group, after initial decreases at 3 or 6 months, at 12 months there were increases in total cholesterol by 5.26 mg/dl (p=0.396), LDL by 8.76 mg/dl (p=0.129) and HDL by 2.26 mg/dl (p=0.012). Only in triglycerol levels was there a sustained decreased at 12 months with a reduction from baseline of 28.89 mg/dl (p=0.119). Level 1+

[36]

Evidence Statement CG66ES8

One RCT16 examined the short-term effects, participants were followed up for 3 months, of a low-carbohydrate diet compared with a reduced portion low-fat diet in obese Type 2 diabetics. There was a significantly larger mean weight reduction in the low-carbohydrate arm (N=51) of their RCT, 3.550.63 kg, than in the low-fat arm (N=51) which showed a mean reduction of 0.920.40 kg (p=0.001). Level 1+

[38]

Evidence Statement CG66ES9

The same RCT reported that glycaemic control improved in both arms of the trial. Improvements were greater in the low-carbohydrate arm, HbA1c decreased from a baseline of 9.000.20%, by 0.550.17%, but this did not reach statistical significance. In the low-fat arm HbA1c decreased from a baseline of 9.110.17% by 0.230.13% (p=0.132). Level 1+

[38]

The risk of arterial disease and microvascular complications in people with diabetes are known to be related to the extent of hyperglycaemia with time. While the lifestyle, oral agent, and injectable therapies discussed in this guideline can improve blood glucose control, their efficacy is limited, as the underlying pathogenesis of diabetes worsens with time. As symptoms are not a reliable guide to blood glucose control in people on therapy, it is important to have an accurate means of measuring blood glucose control over time, to enable decision-making. This section addresses the clinical questions as to the tests of blood glucose control best predictive of future vascular damage from diabetes, the nature of the relationship between test results and such vascular risk, how tests should be deployed in clinical practice, and how they might be interpreted.

Discussion

There were a number of difficulties agreeing the level at which therapeutic interventions should begin or be enhanced. It was agreed that people with diabetes and the professionals advising

Involve patient in decsions on HbA1c target

When setting a target glycated haemoglobin HbA1c: involve the person in decisions about their individual HbA1c target level, which may be above that of 6.5 % set for people with Type 2 diabetes in general encourage the person to maintain their individual target unless the resulting side effects (including hypoglycaemia) or their efforts to achieve this impair their quality of life offer therapy (lifestyle and medication) to help achieve and maintain the HbA1c target level inform a person with a higher HbA1c that any reduction in HbA1c towards the agreed target is advantageous to future health avoid pursuing highly intensive management to levels of less than 6.5 %. '

Evidence Statement CG66ES22

The risk of each of the microvascular and macrovascular complications of Type 2 diabetes and cataract extraction was strongly associated with hyperglycaemia as measured by updated mean HbA1c.

[39]

Evidence Statement CG66ES23

There was no indication of a threshold for any complication below which risk no longer decreased, nor a level above which risk no longer increased.

[39]

Evidence Statement CG66ES24

There was an increase in CV risk with increasing levels of glycosylated haemoglobin in persons with Type 2 diabetes.

[40]

Evidence Statement CG66ES25

There was an independent progressive relationship between GHb and incident cardiovascular events, renal disease and death.

[41]

Evidence Statement CG66ES26

There was an independent graded association between glycaemic control and incidence of hospitalisation and/or death due to heart failure.

[42]

Evidence Statement CG66HES1

The UKPDS included an analysis of intensive blood glucose control with metformin for overweight patients compared to conventional treatment primarily with diet. The study included 753 overweight (>120% ideal body weight) patients with newly diagnosed Type 2 diabetes from 15 hospital-based clinics in England, Scotland and Northern Ireland. Of these patients 342 were allocated to an intensive blood glucose control policy with metformin and 411 were allocated to conventional treatment, primarily with diet alone. The study was conducted from 1977 to 1991. The median follow-up period was 10.4 years.

Evidence Statement CG66HES2

In the conventional policy group the glycaemic goal was to obtain the lowest fasting plasma glucose (FPG) attainable with diet alone. In the intensive policy group the aim was a FPG of less than 6.0 mmol/l by increasing the dose of metformin from 500 to 2,550 mg a day as required. Use of metformin for intensive blood glucose control in overweight patients was found to confer a 32% risk reduction for any diabetes related endpoint and a 42% risk reduction for diabetes related deaths compared with a conventional policy.

Evidence Statement CG66HES3

In the 2001 cost-effectiveness analysis, intensive treatment with metformin cost on average 258 less than conventional treatment, and resulted in a longer life expectancy of 0.4 years.34

Evidence Statement CG66HES4

In the 2005 cost-utility analysis the discounted cost (6% discount rate) of an intensive blood glucose control policy with insulin or sulphonylureas was on average 884 more per patient and the discounted benefits gained were 0.15 quality of life-adjusted year (QALY), a cost per QALY gained of 6,028.33

Evidence Statement CG66HES5

The discounted cost of intensive blood glucose control policy with metformin in overweight patients was on average 1,021 less than the conventional policy and had a longer discounted life expectancy of 0.55 QALYs, making this intensive treatment strategy both cost-saving and more effective.34

Self-monitoring is the only direct method by which a person with diabetes can be aware of their level of control of blood glucose. It has utility when used with therapies of erratic effect, those requiring considerable dose adjustment (notably insulin), and in those whose therapies put them at risk of hypoglycaemia. More controversial, except for people using insulin, is the use of self-monitoring to provide feedback on the impact of lifestyle measures on blood glucose control, and as part of the overall educational package designed to enhance self-care. Indirect monitoring using urine glucose tests is cheaper, but also delivers less information than plasma glucose monitoring. This section addresses the clinical question of the role of self-monitoring of plasma glucose in people at different stages of the condition and on different therapies, and its integration with other key processes of care such as patient education.

Discussion

The newer meta-analyses did not add significantly to the views expressed in the previous Type 2 diabetes guideline. The findings of the ROSSO study44 and the data from the large Kaiser Permanente cohorts 43 added considerable confidence to the view that SMBG was an integral part of effective patient education packages and enabled the effective use of many other therapies and lifestyle interventions. The view in the previous guideline that self-monitoring of plasma glucose is not a stand-alone intervention was endorsed. Concern was expressed over a number of issues surrounding the successful use of selfmonitoring, and recognised that its cost meant that it had to be effectively deployed. It should only be supported in the context of a provision of a package of care, including structured education, from a primary or secondary diabetes care team. The initial education should be provided by a properly trained and skilled professional with understanding of the problems of the technology. Also, the skills of people with diabetes in using the technology should be the subject of regular quality assurance (together with the devices) perhaps as part of the regular annual

review process. Devices should be calibrated to plasma glucose levels in line with 2006 WHO recommendations.

Self monitoring of plasma glucose as part of self-management education

Offer self-monitoring of plasma glucose to a person newly diagnosed with Type 2 diabetes only as an integral part of his or her self-management education. Discuss its purpose and agree how it should be interpreted and acted upon. '

Evidence Statement CG66ES27

Even though the Cochrane reviews37,38 were not able to meta-analyse the data (due to clinical and methodological heterogeneity) the authors concluded that SMBG might be effective in improving glycaemic control in patients with Type 2 diabetes who are not using insulin. Authors also stated that a well designed large RCT assessing the benefits (including patientrelated outcomes) of SMBG alongside patient education is required. Level 1+

[**???**]

[**???**]

Evidence Statement CG66ES28

The other review36 concluded that, in the short term, and when integrated with educational advice, self-monitoring of blood glucose as an adjunct to standard therapy, may contribute to improving glycaemic control among non-insulin requiring Type 2 diabetes patients. Level 1+

[43]

Evidence Statement CG66ES29

In an indirect analysis, Jansen39 found a non-significant reduction in HbA1c of 0.3% when interventions with SMBG were compared with those associated with SMUG. The study by Jansen also reported that interventions with SMBG were found to be more effective in reducing HbA1c than interventions without self-monitoring. The reduction in HbA1c was statistically significant and it was estimated to be around 0.4%. This effect was increased when regular feedback was added to the SMBG and was shown in both an insulintreated Type 2 diabetes group, and in a group of Type 2 diabetes patients that included those being treated with oral agents. Level 1+

[44]

Evidence Statement CG66ES30

An RCT looking at the effects of an education manual41 on blood glucose monitoring found that the greatest reduction in HbA1c occurred in the education manual group (0.131.28%) compared with both the SMBG (0.041.31%) and standard care (0.041.10%) groups. The authors did not report whether there was a significant difference between groups. Level 1+

[45]

Evidence Statement CG66ES31

A second multicentre RCT42 found a significantly greater reduction in HbA1c in the SMBG compared to the non-SMBG group (p=0.0086). Level 1+

[46]

Evidence Statement CG66ES32

A retrospective cohort study performed in the USA (N=976) found that duration of SMBG (03 years) was not a significant predictor of HbA1c values in those with Type 2 diabetes on oral medication.45 Level 2+

[47]

Evidence Statement CG66ES33

In a German retrospective cohort study of 1,609 patients with Type 2 diabetes, hazard ratios indicated that SMBG was associated with a 32% reduction in morbidity for combined macrovascular (MI and stroke) and microvascular (foot amputation, blindness or end-stage renal failure) non-fatal endpoints (HR=0.68, 95% CI 0.510.91, p=0.009). This was despite an increase of microvascular events, and a 51% reduction in mortality over the observation period (HR=0.49, 95% CI 0.310.78, p=0.003) where mean follow-up was 6.5 years. In those not receiving insulin, SMBG was associated with a 28% reduction in combined non-fatal endpoints (HR=0.72, 95% CI 0.520.99, p=0.0496) and a 42% reduction in mortality over the observation period (HR=0.58, 95% CI 0.350.96, p=0.035).44 Level 2+

[48]

Evidence Statement CG66ES34

A retrospective cohort study of people with diabetes in a US medical care programme43 found greater SMBG practice frequency among new users, which

was associated with a graded decrease in HbA1c (relative to non-users) regardless of diabetes therapy ($p<0.001$). Changes in SMBG frequency among prevalent users were associated with an inverse graded change in HbA1c but only among pharmacologically-treated patients ($p<0.0001$). Level 2+

[49]

Evidence Statement CG66ES35

A study including patients from the Fremantle Diabetes Study (FDS) cohort46 over 5 years of follow-up did not find any difference in HbA1c or in fasting plasma glucose, either overall or within treatment groups in patients who used SMBG than those who did not ($p=0.05$). There were also no differences in HbA1c or FPG between SMBG adherent and non-adherent users by treatment group ($p=0.09$). Level 2+

[50]

Evidence Statement CG66ES36

In a qualitative study performed in Scotland of newly diagnosed Type 2 diabetics, patients reported strongly negative views of urine testing, particularly when they compared it with selfmonitoring of blood glucose. Patients perceived urine testing as less convenient, hygienic and accurate than self-monitoring of blood glucose. Most patients assumed that blood glucose meters were given to those with a more advanced or serious form of diabetes. Patients often interpreted negative urine results as indicating that they did not have diabetes.49

[51]

Evidence Statement CG66ES37

A Scottish qualitative study sought newly diagnosed Type 2 diabetes patients perspectives on the pros and cons of SMBG. Pros of self-monitoring: provides a heightened awareness of, and evidence of, the condition when readings are within advised guidelines and fluctuations are easily interpretable, patients emphasise the positive role that monitoring has in their diabetes management. Low readings are a high point giving personal gratification cultivates independence from health services and enhances self-regulation. Cons of self-monitoring: potentially, self-monitoring can raise anxiety about readings blood glucose parameters were found to be problematic by patients when they felt they were receiving contradictory information about upper thresholds or no guidance about ideal parameters lack of awareness as to how to manage hyperglycaemia increased self-responsibility accompanied by increased self-blame and negative emotional reactions to high glucose readings counter-intuitive readings could be sources of distress and

anxiety, in some cases adversely effecting adherence to diabetic regimens by promoting nihilistic attitudes healthcare professionals were not interested in readings.50

[52]

The clinical questions concern the order with which these oral glucose-lowering medications should be introduced and added to one another in different groups of people with Type 2 diabetes. Because such people vary in attributes (such as body weight) which can affect choice of medication, and because some medication side effects can have consequences for aspects of daily living (such as driving motor vehicles), blanket recommendations cannot be made for everyone with Type 2 diabetes.

Discussion

None of the newer evidence altered the priority given to metformin cited in the previous guideline. Although the specific cardioprotective effects of metformin suggested by the UKPDS study were open to challenge from some of the very recent studies, this was not on the basis of strong outcome data. Large observational studies from Canada and Scotland111,112 appeared to support the widespread advantage of metformin over sulfonylureas, but the A Diabetes Outcome Progression Trial (ADOPT) study did not. The cardioprotective gains shown in the UKPDS andin the Scottish study far outweighed the concerns over lactic acidosis (provided renal function was adequate) in people with mild to moderate hepatic and cardiac disease. Nearly all the data related to overweight people, and there was little to guide metformin use in the normal weight person without extrapolation of the evidence. However, the overwhelming majority of people with Type 2 diabetes are overweight; in making this judgement however attention has to be paid to differences between ethnic groups.

Metformin treatment for overweight people

Start metformin treatment in a person who is overweight or obese (tailoring the assessment of body weight associated risk according to ethnic group*) and whose blood glucose is inadequately controlled (see recommendation 16) by lifestyle interventions (nutrition and exercise) alone. ’

Evidence Statement CG66ES38

In terms of mortality and morbidity, a Cochrane review56 looked at the events listed in the Clinical Endpoint Analyses from the UKPDS* (UKPDS-34 1998). The systematic review found five studies providing data on mortality and/or morbidity outcomes (four RCTs in addition to the UKPDS).

[???]

Evidence Statement CG66ES39

In the UKPDS (median follow-up 10.7 years), among overweight (54% with obesity) participants allocated to intensive blood glucose control, metformin (N=342) showed a greater benefit than chlorpropamide, glibenclamide, or insulin (N=951) for any diabetes-related outcomes, and for all-cause mortality. For other outcomes including diabetes-related death, MI, stroke, peripheral vascular disease and microvascular, there were no significant differences between both comparison arms. Level 1++

[**???**]

Evidence Statement CG66ES40

In the same vein, the UKPDS found that overweight participants assigned to intensive blood glucose control with metformin (N=342) showed a greater benefit than overweight patients on conventional treatment (non-intensive blood glucose control, mainly with diet), (N=411), for any diabetes-related outcomes, diabetes-related death, all-cause mortality, and MI. For the rest of the outcomes such as stroke, peripheral vascular disease and microvascular, there were no significant differences between both comparison arms. Level 1++

[**???**]

Evidence Statement CG66ES41

After pooling data from the four non-UKPDS trials, the Cochrane review did not find significant differences among comparisons either for all-cause mortality or for ischemic heart disease (study durations ranged from 24 weeks to 2 years). Level 1++

[**???**]

Evidence Statement CG66ES42

Overall, the evidence appraised suggested that monotherapy with metformin produced significantly greater improvements in glycaemic control (i.e. HbA1c and FPG/fasting blood glucose (FBG)) when it was compared with placebo, diet and sulfonylureas. Head-to-head comparisons with other antidiabetic agents (i.e. alpha-glucosidase inhibitors, thiazolidinediones, meglitinides and insulin) and extended-release formulations of metformin, failed to show more benefit for glycaemic control than standard monotherapy with metformin. In addition metformin used in combination with different doses of nateglinide produce significantly lower glycaemic values than metformin monotherapy.

[**???**]

Evidence Statement CG66ES43

Overall, the evidence demonstrated a significant difference in terms of body weight/BMI reduction favouring metformin monotherapy when compared with sulfonylureas, glitazones and insulin therapies. Non-significant differences were found in head-to-head comparisons between metformin against placebo, diet, alpha-glucosidase inhibitors, meglitinides and treatment with extend-release formulation of metformin. Combination of metformin and different doses of nateglinide produced a significant reduction in body weight when compared with metformin monotherapy. Level 1+

[**???**]

Evidence Statement CG66ES44

Non-significant differences in terms of lipid profile were found when metformin was compared with placebo or meglitinides. Level 1++

[**???**]

Evidence Statement CG66ES45

Studies evaluating other comparisons found differences in specific lipid profile parameters. When compared to diet, metformin significantly reduced total cholesterol (TC), however in a comparison with a a-glucosidase inhibitor, metformin significantly increased TC.56 Level 1++

[**???**]

Evidence Statement CG66ES46

The meta-analysis of studies comparing metformin to sulfonylureas found significant benefits for metformin in terms of low-density lipoprotein cholesterol (LDL-C) and triglycerides.56 Level 1++

[**???**]

Evidence Statement CG66ES47

In a comparison of metformin against insulin, significant benefits for metformin were found in terms of total and LDL-C levels but not high-density lipoprotein cholesterol (HDL-C).56 Level 1++

[**???**]

Evidence Statement CG66ES48

In a study which compared metformin with pioglitazone,59 pioglitazone was significantly more beneficial in terms of triglycerides and HDL-C, however metformin was more beneficial for LDL-C levels. The TC/HDL-C ratio did not differ significantly between the groups. Level 1++

[53]

Evidence Statement CG66ES49

A study which compared metformin monotherapy with metformin and nateglinide63 found no differences across the lipid profile between these two groups except for triglycerides which were reduced significantly in the metformin and nateglinide group (nateglinide 120 mg tablets thrice daily). Level 1+

[54]

Evidence Statement CG66ES50

Where MIR was compared with MXR treatment, lipid profiles were similar between groups (statistical significance not reported) except for triglycerides where the mean change from baseline in the immediate-release group was 1 mg/dL; but was 34 mg/dl in the MXR 1,000 mg arm, and 42 mg/dl in the MXR 1,500 mg arm.65 Level 1+

[55]

Evidence Statement CG66ES51

The main differences across all the different treatment groups were: the high frequency of gastrointestinal (GI) complaints reported by metformin-treated patients the high frequency of hypoglycaemic events reported by sulfonylurea-treated patients the high number of episodes of oedema reported by glitazone-treated patients the high number of cases of upper respiratory infection in patients treated with meglitinides. Level 1+

[**???**]

[53]

[56]

[54]

[57]

[55]

Evidence Statement CG66ES52

In the only RCT65 directly comparing MIR and MXR, more diarrhoea, flatulence and abdominal pain were experienced in the extended-release group whilst more or equivalent proportions of patients, experienced nausea/vomiting, headache and dyspepsia/heartburn in immediate-release group (significance tests not performed). In placebo-controlled studies, patients on MXR always experienced more GI AEs than those on placebo.66 Level 1+

[55]

[58]

Evidence Statement CG66ES53

A retrospective chart review67 found a significantly reduced frequency of GI AE in a cohort of patients when they were switched from MIR to MXR. A cohort of patients taking metformin for the first time also experienced less GI AEs if they were commenced on MXR rather than the immediate-release formulation. Level 2+

[59]

Evidence Statement CG66ES54

A Cochrane review57 looked at the risk of lactic acidosis in patients treated with metformin. There were no cases of fatal or non-fatal lactic acidosis reported. Level 1+

[**???**]

Evidence Statement CG66ES55

In addition, one RCT58 did not find a significant difference in plasma lactate levels between

[60]

Evidence Statement CG66HES6

metformin-treated patients and patients treated with other antidiabetic agents. Level 1+

Evidence Statement CG66HES7

If additional costs of intensive policy with metformin were 50% more than assumed in the baseline estimates then the cost per life-year gained would be 948.

Evidence Statement CG66HES8

In the cost-utility model there was a 77% probability that metformin would prove to be cost-saving compared with a conventional policy.33 Sensitivity analyses were performed for anti-diabetic therapy cost (50%); standard practice costs (50%); cost of complications (50%); utility of one when free of complications; no treatment benefit and continuing benefit beyond the trial. Metformin was consistently shown to be a cost-reducing intervention.

The clinical questions concern the order with which these oral glucose-lowering medications should be introduced and added to one another in different groups of people with Type 2 diabetes. Because such people vary in attributes (such as body weight) which can affect choice of medication, and because some medication side effects can have consequences for aspects of daily living (such as driving motor vehicles), blanket recommendations cannot be made for everyone with Type 2 diabetes.

Discussion

The evidence base for the insulin secretagogues was more extensive than ascertained for the parent guideline. However, in many of the papers in which they are compared to other drugs they were being used as the comparator therapy rather than the investigated therapy. New evidence did not lead to new conclusions about the role of these drugs in clinical management, either from the point of view of efficacy or safety. Sulfonylureas proved as efficacious as newer comparator therapies in reducing surrogate outcomes (principally HbA1c) highlighting that they still have a role in modern management of Type 2 diabetes. In the ADOPT study54 the sulfonylurea glibenclamide controlled HbA1c as effectively as rosiglitazone or metformin as monotherapy for the first 3 years, but persistence of glucose control after this time was worse. Cardiovascular outcomes were, if anything, better with the sulfonylurea.

When to consider sulfonylurea as first line therapy

Consider a sulfonylurea as an option for first-line glucose lowering-therapy if: the person is not overweight, the person does not tolerate or is contraindicated , a rapid response to therapy is required because of hyperglycaemic symptoms. ’

Evidence Statement CG66ES56

Overall, metiglinides produced a significantly greater glycaemic control and a higher incidence of hypoglycaemic events when compared with placebo. No differences were found in terms of body weight and lipid profile.

[61]

[62]

[63]

Evidence Statement CG66ES57

When repaglinide was compared with nateglinide in people with Type 2 diabetes previously treated with diet and exercise: repaglinide and nateglinide had similar postprandial glycaemic effects. However, repaglinide was more effective than nateglinide in reducing HbA1c and FPG values a greater weight gain (p=0.04) was seen in repaglinide-treated patients when compared to nateglinide-treated patients hypoglycaemic events were more frequently reported by patients receiving repaglinide (non-significant difference between the two groups).

[61]

[62]

[63]

Evidence Statement CG66ES58

In head-to-head comparisons with sulfonylureas, metiglinides failed to demonstrate better glucose control and led to a similar number of hypoglycaemic events. No significant differences were observed in terms of lipid profile and body weight reduction.

[64]

[65]

[66]

Evidence Statement CG66ES59

When a modified-release version of gliclazide was compared with the immediate-release version of gliclazide in people with Type 2 diabetes who had been on diet control or ontreatment with oral hypoglycaemic agents:both versions were associated with significant reductions in HbA1c (non-significant difference between the two groups). FPG decreased significantly on gliclazide MR but not

on gliclazide (non-significant difference between the two groups) no clinically significant changes were seen in terms of lipid profile (non-significant difference between the two groups) hypoglycaemic events were only reported by patients receiving gliclazide MR (9%) (nonsignificant difference was reported between the two groups).

[53]

Evidence Statement CG66ES60

When a modified-release version of gliclazide was compared with glimepiride in people with Type 2 diabetes being treated with diet alone or with either metformin or alpha-glucosidase inhibitors:both interventions were equally effective in terms of glycaemic control (alone or in combination with metformin or alpha-glucosidase inhibitors) gliclazide MR had a better safety profile than glimepiride.

[67]

Evidence Statement CG66ES61

When insulin lispro was compared with glibenclamide in people with Type 2 diabetes who had been treated with oral antidiabetic (OAD) therapy, but not insulin: both regimes produced comparable effects in the control of glycaemia with respect to HbA1c. However, treatment with insulin lispro resulted in smaller postprandial blood glucose excursions compared to oral treatment with glibenclamide no significant differences were observed between the treatment groups regarding hypoglycaemic episodes and other AEs.

[68]

Evidence Statement CG66ES62

When repaglinide was compared with gliclazide (both drugs in combination with bedtime NPH) in Type 2 diabetes patients inadequately controlled with oral hypoglycaemic therapy: both interventions were associated with significant reductions in HbA1c and FPG (nonsignificant difference between the two groups) weight gain during the treatment period was similar in both groups no significant differences were observed between the treatment groups regarding hypoglycaemic episodes and other AEs.

[69]

Evidence Statement CG66ES63

Nateglinide in combination with metformin was compared with gliclazide and metformin, to compare the effects on glycaemic control in patients with Type 2 diabetes: no significant difference was seen between the groups in terms of HbA1c the nateglinide group demonstrated better PPG control.

[70]

Evidence Statement CG66ES64

When glimepiride in combination with metformin was compared with monotherapy of each drug in Type 2 diabetes patients inadequately controlled by metformin monotherapy: combination treatment was more effective than either drug alone in terms of glycaemic control combination therapy was more effective than either drug in reducing TC levels metformin alone resulted in a significantly lower BMI than either glimepiride alone, or the combination the incidence of hypoglycaemic episodes was significantly higher in the combinationtreatment group than in either of the monotherapy groups.

[71]

Evidence Statement CG66ES65

When nateglinide in combination with metformin was compared with monotherapy of each treatment and placebo in drug naive patients with Type 2 diabetes: nateglinide, metformin and combination therapy (nateglinide + metformin), were associated with significant reductions in HbA1c, FPG and PPGE (an additive effect was seen with combination therapy) the incidence of GI AEs was higher in patients receiving combination therapy and metformin than in those receiving placebo and nateglinide the incidence of hypoglycaemic episodes was higher in the combination treatment group than in either of the monotherapy groups.

[70]

Evidence Statement CG66ES66

The effect of adding nateglinide to therapy with insulin glargine in adults with Type 2 diabetes previously treated with insulin and with poor blood glucose controlAdding nateglinide improved blood glucose control in the early part of the day afterbreakfast and lunch. Adding nateglinide did not provide good blood glucose control overall.

[70]

Evidence Statement CG66ES67

This cohort study investigated the incidence of hypoglycaemia in patients treated with diet alone, sulphonylurea, metformin or insulin monotherapy. The results on metformin are not discussed here as they are considered in a separate question.

[72]

Evidence Statement CG66HES10

In a further cost-utility analysis published in 2005 intensive blood glucose control with insulin or sulfonylurea was found to have a cost-effectiveness ratio of 6,028 per QALY gained compared to conventional glucose (2004 cost year, 3.5%).33

[73]

Evidence Statement CG66HES9

Conventional glucose control, mainly through diet was compared to more intense blood glucose control with insulin or sulfonylureas in the UKPDS. Intensive treatment was costsaving with the resource use according to the trial protocol. Using standard clinical resource use, intensive treatment had an incremental cost-effectiveness ratio (ICER) of 1,166 per eventfree year gained within the trial period (6% discount rate, 1997 cost year).98

The clinical questions concern the order with which these oral glucose-lowering medications should be introduced and added to one another in different groups of people with Type 2 diabetes. Because such people vary in attributes (such as body weight) which can affect choice of medication, and because some medication side effects can have consequences for aspects of daily living (such as driving motor vehicles), blanket recommendations cannot be made for everyone with Type 2 diabetes.

Discussion

The newer evidence did not add significantly to the previous understanding of the role ofa-glucosidase inhibitors in the management of Type 2 diabetes, except in so far as the evidence suggested that the efficacy and intolerance problems were similar in oriental ethnic groups toEuropids. Lower glucose-lowering efficacy, a higher rate of intolerance and dropout fromtherapy, and relative expense compared to generic metformin and sulfonylureas were noted.However, hypoglycaemia is not a problem when this drug is used as monotherapy, though through glucose lowering it may enhance the hypoglycaemic potential of other medications.

When to consider acarbose

Consider acarbose for a person unable to use other oral glucose-lowering medications. ’

Evidence Statement CG66ES68

The evidence appraised suggested that acarbose (used as monotherapy or in combination) failed to demonstrate better glycaemic control when compared with other oral agents. Treatment with acarbose did not demonstrate superiority over other oral agents when lipid profile and body weight were evaluated.

[74]

[**???**]

[75]

[75]

[75]

[75]

[75]

[75]

[75]

Evidence Statement CG66ES69

Reports of adverse effects were higher in the acarbose groups across all studies.99,101106 The main difference between the treatment groups was the high frequency of GI complaints reported by acarbose-treated patients. Flatulence was reported in all acarbose arms ranging from 28.6% to 57.5% of all patien

[74]

[**???**]

[75]

[75]

[75]

[75]

[75]

[75]

[75]

Insulin was previously normally delivered from syringes, necessitating accurate measuring of insulin doses drawn up from insulin vials under suitably hygienic conditions. Modern peninjector devices obviate most of the problems of measuring up doses while avoiding most of the hygiene problems, and offer a convenient and safe means of carrying around injectionequipment. However, several models of injector are available, including some designed for those with visual and physical impairments. The clinical question addressed here was whether any particular pen-injector had an evidencebased advantage over any other, including groups of people with difficulty using such devices.

Discussion

There was no strong published evidence that insulin pen injectors were a preferred option forinsulin injection, but in clinical practice this was not questionable. The studies comparing devices did not compare all devices, were inevitably unblinded, and were manufacturer sponsored in single centres for the most part. The issue of bias was real. It was considered thatsome devices preformed better than others, but also that this was generally known to regular prescribers. Prescribers should be fully familiar with the devices they were recommending; this would be difficult for all the devices available. One injection device, the InnoLet, was not a pen injector, but was aimed more at people withphysical disabilities in manipulating injection systems. The studies were consistent with clinical experience in suggesting that this device was successful in enabling self-injection in somepeople who could not otherwise do it easily or reliably. Please refer to the Diabetes UK guidance for the issue of disposal of devices/sharps.

Education for those requiring insulin via injection device

Offer education to a person who requires insulin about using an injection device (usually a pen injector and cartridge or a disposable pen) that they and/or their carer find easy to use. ’

People with Type 2 diabetes are at high cardiovascular (CV) risk, high risk of diabetes eye damage, and high risk of renal disease. These adverse outcomes are known to be reduced by improved blood pressure (BP) control, which can be used to lower the risk of stroke, MI, blindness and renal failure.226 Some other forms of diabetes microvascular damage, including peripheral nerve damage, are known to be associated with higher BP.227 BP lowering is likely to be highly cost-effective in people with Type 2 diabetes, more so than in the general population. A number of clinical questions then face the person with diabetes and their advisors, these include: at what levels of BP to initiate therapy whether, and to what extent, those levels should be influenced by particular risk factors(in particular those involved in renal disease) what level of BP to aim for, and whether that should be modified by the presence of renal, eye, or macrovascular damage, what lifestyle measure are effective and cost-effective in lowering BP

what pharmacological interventions are effective and cost-effective in BP lowering how choice of agent might be modified by the presence of end organ damage. Lifestyle measures (explored elsewhere) and monotherapy medication are known to have limited efficacy in lowering BP. Additional clinical questions arise over: the combinations of medications to be used after first-line therapy considerations including synergies of action, side effects of some combinations, and cost.

Discussion

The GDG noted the problems in assigning BP lowering targets in this area, and in particular the problem setting a cut-off where the evidence suggests the lower the blood pressure the better (without adverse effects) difficulties of achieving any reasonable target in some people individual targets that should logically vary with individual risk arbitrary dichotomy that arises immediately above and below any target level. The results of some RCTs suggested that SBP well into the normal range (below usual target values) was both achievable and associated with benefit in people with Type 2 diabetes, consistent with epidemiological evidence from other studies. In some other studies tight BP control seemed difficult to achieve, consistent with the groups clinical experience. This led the group to take a simple risk approach centered on a target level of <140/80 mmHg for most people with Type 2 diabetes, and <130/80 mmHg for those at more particular risk. The latter group included people with raised albumin excretion rate (AER) (microalbuminuria or worse), eGFR <60 ml/min/1.73 m2, those with retinopathy, and those with prior stroke or transient ischaemic attack (TIA). The concern that more active prevention was being targeted at those who had already developed end-organ damage was recognised, but it was noted that for both microalbuminuria (chapter 16) and early retinopathy (chapter 17) the recommendations on annual surveillance meant that markers of damage would be detected many years before ill health ensued.

When to add medications to lifestyle advice

Add medications if lifestyle advice does not reduce blood pressure to below 140/80 mmHg (below 130/80 mmHg if there is kidney, eye or cerebrovascular damage). ’

Evidence Statement CG66ES100

The Cochrane review, antihypertensive agents for preventing diabetic kidney disease, identified that ACEI compared with placebo/no treatment reduced the development of microalbuminuria, and ACEI compared with CCB reduced the risk of developing kidney disease.236

[76]

Evidence Statement CG66ES101

The meta-analysis identified that an ACEI or A2RB compared with other treatments only showed significant reduction in UAER.238

[77]

Evidence Statement CG66ES102

The HOPE study identified that ramipril compared with placebo reduced the risk of new microalbuminuria and that both new microalbuminuria and progression of proteinuria was higher for the diabetic group than the non-diabetic group.240

[**???**]

Evidence Statement CG66ES103

The combination of lisinopril and telmisartan identified higher reduction with AER compared with the monotherapies.243

[78]

Evidence Statement CG66ES104

The combination of fosinopril + amlodipine reduced UAE compared with amlodipine monotherapy (all time points) and with fosinopril monotherapy (after 18 months).245

[79]

Evidence Statement CG66ES105

The extended HOPE trial identified that at the end of the extension phase there was a significant further reduction in risk for diabetes for ramipril vs placebo (2.7% vs 4.0%, RR 0.66, 0.46 to 0.95).241 Level 1+

[80]

Evidence Statement CG66ES106

The study which considered fosinopril and amlodipine monotherapy, and in combination, found that HbA1c was NS changed by any treatments and body weight remained unchanged.245 Level 1+

[79]

Evidence Statement CG66ES107

The study which compared verapamil SR + trandopril and atenolol + chlorthalidone found that HbA1c remained stable with verapamilSR + trandopril but increased with atenolol + chlorthalidone 7.8 (1.26) at baseline and 8.6 (1.77) at last visit, treatment difference, p=0.0001; fasting glucose and fructosamine treatment difference, p=0.0001.249 Similarly, fasting glucose and fructosamine remained stable with verapamil SR + trandopril but increased with atenolol + chlorthalidone, treatment difference p=0.0001.249 Level 1++

[81]

Evidence Statement CG66ES108

The study which considered verapamil + trandopril vs enalapril + hydrochlorothiazide identified that HbA1c remained stable with verapamil + trandopril but increased with enalapril + hydrochlorothiazide (baseline 5.961.25% to final 6.411.51%), difference between groups, p=0.040.248 Crude blood glucose changes were 2369 mg/dl for verapamil + trandopril (16.8% reduction) and 132 mg/dl (0.8% reduction) with enalapril + hydrochlorothiazide. The percentage of participants with glycaemic control (<126 mg/dl) increased from 50% to 72% with verapamil + trandopril, but did not change with enalapril + hydrochlorothiazide.248 Level 1++

[82]

Evidence Statement CG66ES109

Both Cochrane reviews identified an increased risk of cough with ACE vs placebo/no treatment (four trials, N=3,725, RR 1.79, 1.19 to 2.69),236 (10 trials, N=7,087, RR 3.17, 2.29 to 4.38).237 Level 1++

[76]

[@2005]

Evidence Statement CG66ES110

Throughout the other studies the incidence of discontinuation due to AEs was small and the AEs reported were mainly; progression of diabetes, unsatisfactory therapeutic response, hypotension, ankle oedema, tachycardia, headache, cough, nausea, stomach upset, respiratory infection, and dizziness. Level 1+

[76]

[@2005]

[77]

[???]

[???]

[80]

[78]

[78]

[@2005]

[79]

[83]

[84]

[82]

[81]

Evidence Statement CG66ES111

In summary, A2RB therapy was associated with greater benefits for Type 2 diabetes patients in terms of renal outcomes (e.g. progression to ESRD, doubling of serum creatinine, proteinuria) than treatment with placebo, CCB or sympatholytic agents. In addition, treatment with A2RB was also associated with a better metabolic and BP profile than sympatholytic therapy but nonsignificant differences were observed over those treated with CCB.

[@2005]

[85]

[86]

[87]

[88]

[89]

[90]

[91]

[92]

[93]

Evidence Statement CG66ES112

A Cochrane review237 did not find a statistically significant reduction in the risk of all-cause mortality in the five studies (3,409 patients) of A2RB vs placebo/no treatment. RR 0.99, 95% CI 0.85 to 1.17. Level 1++

[@2005]

Evidence Statement CG66ES113

A post hoc analysis254 compared the incidence of hospitalisation for heart failure within three tertiles of baseline serum creatinine concentration (highest, 2.1 to 3.6 mg/dl; middle, 1.6 to 2.0 mg/dl; lowest, 0.9 to 1.6 mg/dl). The study reported that the crude incidence of first hospitalisations for heart failure was higher in the highest (16.4%) and middle (15.0%) tertiles than in the lowest (11.1%) tertile (trend test across tertiles, p=0.02). The study concluded that losartan decreased the hospitalisations for heart failure by 50.2 and 45.1, in the highest and middle tertile, respectively but was associated with a non-significant increased risk (42.5%) of hospitalisations in the lowest tertile. Level 1+

[85]

Evidence Statement CG66ES114

A Cochrane review237 found a significant reduction in the risk of ESRD with A2RB compared to placebo/no treatment (three studies, N=3,251): RR 0.78, 95% CI 0.67 to 0.91. Level 1++

[@2005]

Evidence Statement CG66ES115

A post hoc analysis254 compared the incidence of ESRD within three tertiles of baseline serum creatinine concentration (highest, 2.1 to 3.6 mg/dl; middle, 1.6 to 2.0 mg/dl; lowest, 0.9 to 1.6 mg/dl). The study reported that the observed crude incidence of ESRD was significantly higher in the highest (40.5%) and middle (19.3%) tertiles as compared with the lowest (7.3%) tertile (trend test across tertiles, p<0.0001). The study concluded that losartan decreased the risk of ESRD by 24.6, 26.3, and 35.3% in highest, middle, and lowest tertiles respectively. Level 1+

[85]

Evidence Statement CG66ES116

A Cochrane review237 found a significant reduction in the risk of doubling of serum creatinine concentration with A2RB compared to placebo/no treatment (3 studies, 3,251 patients): RR 0.79 95% CI 0.67 to 0.93. Level 1++

[@2005]

Evidence Statement CG66ES117

A Cochrane review237 showed that the use of A2RB versus placebo/no treatment was also associated with a significant reduction in the risk of progression from micro- to macroalbuminuria (three studies, 761 patients); RR 0.45, 95% CI 0.32 to 0.75. Level 1++

[@2005]

Evidence Statement CG66ES118

A Cochrane review237 found a significant increase in regression from micro- to normoalbuminuria with A2RB versus placebo/no treatment (16 studies, 1,910 patients) RR 1.42, 95% CI 1.05 to 1.93. Level 1++

[85]

Evidence Statement CG66ES119

A post hoc analysis254 compared the median proteinuria reduction (%) within three tertiles of baseline serum creatinine concentration (highest, 2.1 to 3.6 mg/dl; middle, 1.6 to 2.0 mg/dl; lowest, 0.9 to 1.6 mg/dl). The study showed a significantly ($p<0.0001$) greater median percentage proteinuria reduction (versus baseline) on losartan than on placebo in the highest (24 vs 8%), middle (16 vs 8%), and lowest (15 vs 10%) tertiles respectively. Level 1+

[87]

Evidence Statement CG66ES120

A post hoc analysis of the IRMA study255 reported that after 2 years of follow-up UAER decreased by 34% (95% CI 8 to 53), and 60% (95% CI 46 to 70) in the irbesartan 150 mg and irbesartan 300 mg groups respectively ($p<0.05$ vs baseline). No significant reductions in UAER were found in patients receiving placebo. One month after withdrawal of irbesartan therapy, the same post hoc analysis255 found no significant increases in UAER in patients receiving placebo or irbesartan 150 mg when compared with baseline values. However, the study

reported that UAER remained persistently reduced by 47% (95% CI 24 to 63) in the irbesartan 300 mg group ($p<0.05$ vs baseline). This persistent reduction in the irbesartan 300 mg group, as compared with baseline, was highly significantly different from irbesartan 150 mg ($p<0.01$). This difference occurred although the regain in GFR between the two irbesartan groups were nearly identical. Level 1+

[87]

Evidence Statement CG66ES121

A post hoc analysis of the IRMA study255 found that after 2 years of treatment there were no significant differences in mean arterial blood pressure between patients treated with placebo or irbesartan (150 or 300 mg). However, 1 month after withdrawal of irbesartan therapy mean arterial blood pressure was unchanged in the placebo group, but increased significantly in the irbesartan groups to 1092 and 1082 in the 150 mg and 300 mg groups respectively ($p<0.01$). Level 1+

[86]

Evidence Statement CG66ES122

A post hoc analysis of the RENAAL study253 found no significant differences between patients treated with losartan or placebo in terms of glycaemic levels, lipid profile or serum uric acid after 3.4 years of follow-up. Level 1+

[@2005]

Evidence Statement CG66ES123

A Cochrane review237 found a significant increase in the risk of hyperkalaemia with A2RB compared to placebo/no treatment (two studies, 194 patients); RR 4.93, 95% CI 1.87 to 15.65. A2RB were not found to be associated with an increased risk of cough compared to placebo/no treatment. Level 1++

[88]

Evidence Statement CG66ES124

One RCT257 with a follow-up of 2.6 years, found that treatment with irbesartan significantly reduced the risk of doubling serum creatinine concentration, development of ESRD, or death from any cause, by 23% compared to the amlodipine therapy ($p=0.006$). Level 1++

[88]

Evidence Statement CG66ES125

When individual endpoints were analyzed the RCT257 reported: A significantly lower risk of a doubling in the serum creatinine concentration in patients receiving irbesartan compared to amlodipine-treated patients (37% lower in the irbesartan group than in the amlodipine group, p< 0.001). Non-significant differences in terms of progression to ESRD between irbesartan-treated patients and those receiving amlodipine (risk 23% lower in the irbesartan group p=0.07). Non-significant difference in the rates of death from any cause between patients treated with irbesartan and those treated with amlodipine. Level 1++

[88]

Evidence Statement CG66ES126

The same study257 did not find a significant benefit associated with irbesartan as compared with amlodipine in reducing the secondary composite endpoint of death from CV causes, nonfatal MI, heart failure resulting in hospitalisation, a permanent neurologic deficit caused by a cerebrovascular event, or lower limb amputation above the ankle. Level 1++

[89]

Evidence Statement CG66ES127

An RCT258 comparing therapy with valsartan and amlodipine reported results for a prespecified subgroup of Type 2 diabetes patients and found non-significant differences between the two treatment arms for the primary composite cardiac outcome which looked at cardiac mortality and morbidity.* Level 1+

[90]

Evidence Statement CG66ES128

Another RCT252 which also compared treatment with valsartan and amlodipine, found that after 24 weeks there was a significant reduction in UAER in patients receiving valsartan as compared with those treated with amlodipine (p<0.001; 95% CI for ratio, 0.520 to 0.710). The UAER at 24 weeks with valsartan was 56% (95% CI, 49.6 to 63.0) of baseline, equivalent to a 44% reduction. The UAER for amlodipine at week 24 was 92% (95% CI, 81.7 to 103.7) of baseline, a reduction of only 8%. Level 1++

[90]

Evidence Statement CG66ES129

The same RCT252 showed a significantly greater percentage of patients returning to normoalbuminuria status by week 24 with valsartan (29.9%) than with amlodipine (14.5%). Treatment difference 15.4% 95% CI, 5.6 to 25.8, $p<0.001$. Level 1++

[88]

Evidence Statement CG66ES130

One RCT257 did not find significant differences in mean arterial pressure in patients treated with irbesartan and amlodipine after 2.6 years of follow-up. Level 1++

[91]

Evidence Statement CG66ES131

One RCT251 reported that at 12 months there were no significant changes from baseline in HbA1c, FPG, BMI, triglycerides and high-density lipoprotein cholesterol (HDL-C) in patients treated with telmisartan or nifedipine gastrointestinal therapeutic system (nifedipine GITS) and there were no significant differences in any of these parameters between treatments. Level 1+

[91]

Evidence Statement CG66ES132

The same RCT251 showed that reduction in total cholesterol and low-density lipoprotein with telmisartan were significantly greater than those with nifedipine GITS ($p<0.05$). Level 1+

[88]

Evidence Statement CG66ES133

One RCT257 reported that the incidence of hyperkalaemia (necessitating discontinuation of the study medication) was significantly higher in patients receiving irbesartan as compared to those receiving amlodipine. Level 1++

[90]

Evidence Statement CG66ES134

One RCT252 found that ankle oedema occurred significantly less frequently in valsartan-treated patients compared to those treated with amlodipine (1.2% vs 7.4% difference 6.2% 95% CI 12.9% to 0.4%, p<0.006). Level 1+

[92]

Evidence Statement CG66ES135

One RCT256 with a follow-up of 4.7 years found that treatment with losartan significantly reduced the risk of CV death, stroke, or MI compared to atenolol therapy. RR 0.76 (95% CI 0.58 to 0.98), p=0.031. Level 1++

[92]

Evidence Statement CG66ES136

When individual endpoints were analysed the RCT256 reported: a statistically significant reduction in the risk of all-cause mortality in losartan-treated patients compared to those receiving atenolol. RR 0.61 (95% CI 0.45 to 0.84), p=0.002 a statistically significant reduction in the risk of CV death favouring the losartan group RR 0.63 (95% CI 0.42 to 0.95), p= 0.028 non-significant difference in the incidence of stroke or MI between patients treated with losartan and those treated with atenolol.

[93]

Evidence Statement CG66ES137

One RCT250 found that after 12 months, patients treated with irbesartan had significantly lower SBP and DBP levels as compared to those receiving doxazosin, (p<0.05). Level 1+

[93]

Evidence Statement CG66ES138

One RCT250 found significantly lower HbA1c levels in doxazosin-treated patients as compared to patients receiving irbesartan after 12 months of follow-up. Level 1+

[93]

Evidence Statement CG66ES139

The same RCT250 found that patients treated with doxazosin had significantly higher levels of HDL-C as compared to those treated with irbesartan ($p<0.05$). Level 1+

[92]

Evidence Statement CG66ES140

One RCT256 showed that albuminuria was reported less frequently ($p=0.002$) as an AE in the losartan than in the atenolol group (losartan 7% vs atenolol 13%). Level 1++

[92]

Evidence Statement CG66ES141

The same RCT256 found that chest pain was more frequently reported in the losartan arm ($p=0.036$) (losartan 2% vs atenolol 8%). Level 1++

[94]

Evidence Statement CG66ES142

The evidence appraised suggested that treatment with beta-blockers in patients with Type 2 diabetes failed to demonstrate a better CV profile when compared with CCB therapy. Furthermore a landmark RCT showed a significant reduction in the incidence of CV outcomes in patients receiving CCB as compared with those treated with beta-blockers. In terms of BP173 12 Blood pressure therapy * BP reduction with all hypertensive treatments was a consistent feature of the studies and therefore only studies where there were significant differences between the treatments will be highlighted. control, the evidence did not demonstrate differences between beta-blocker therapy and other antihypertensives.

[95]

[96]

[97]

[98]

Evidence Statement CG66ES143

All reported CV outcomes were for beta-blockers vs CCBs. For the study considering COER verapamil and atenolol or hydrochlorothiazide there was NS

difference between the groups for both the composite of acute MI, stroke or CV related death and also for the incidence of any component of the composite in the diabetic subgroup.261 Level 1+

[97]

Evidence Statement CG66ES144

The ASCOT-BPLA study found that for the diabetes subgroup for total CV events and procedures there was significantly lower occurrence with the amlodipine based group vs the atenolol based group (HR 0.87, 0.76 to 0.99, p=0.0283), this was also found for the nondiabetic study participants.262 Level 1++

[98]

Evidence Statement CG66ES145

The INVEST study found NS difference in the treatments (verapamilvSR and atenolol) for death or first occurrence of non-fatal MI or non-fatal stroke in both the diabetic and nondiabetic groups.259 Level 1+

[95]

Evidence Statement CG66ES146

Within all the papers included that reported BP outcomes the treatments reduced BP and there was NS difference found between the treatment groups.260262

[96]

[97]

[98]

Evidence Statement CG66ES147

Only the study comparing two beta-blockers reported on renal outcomes. The study considering carvedilol and metoprolol found that carvedilol reduced the albumin:creatinine ratio vs metoprolol (relative reduction 16%, p=0.003).260 This study also identified those with albuminuria of 30 mg or less at baseline, fewer in the carvedilol group vs the metoprolol group progressed to microalbuminuria (6.4%, 25/388 vs 10.3%, 56/542), or from carvedilol vs metoprolol, 0.60, 0.36 to 0.97, p=0.04).260 Level 1++

[96]

Evidence Statement CG66ES148

Only the study comparing two beta-blockers reported on metabolic outcomes. The study considering carvedilol and metoprolol found that carvedilol treatment had no HbA1c changes from baseline while metoprolol increased HbA1c. The mean difference was 0.12%, p=0.006. More participants withdrew due to worsening glycaemic control with metoprolol (16/737, 2.2%) than with carvedilol (3/498, 0.6%), p=0.04.260 Level 1++

[96]

Evidence Statement CG66ES149

The study comparing COER verapamil with atenolol or hydrochlorothiazide261 reported that participants assigned COER verapamil withdrew more often due to adverse signs or symptoms compared with those assigned atenolol of hydrochlorothiazide (p=0.02); the most common reason was constipation (216 in the COER verapamil compared with 28 in the atenolol of hydrochlorothiazide group). However, fewer participants assigned COER verapamil (N=115) atenolol of hydrochlorothiazide withdrew because of poor BP control compared with those assigned atenolol of hydrochlorothiazide (N=207) (p<0.001 by log-rank). Level 1+

[97]

Evidence Statement CG66ES150

The INVEST study259 showed that verapamil and atenolol were generally well tolerated in each treatment group. Patients in the verapamil group reported constipation and coughs more frequently than patients in the atenolol group, while atenolol-treated patients had more dyspnoea, lightheadedness, symptomatic bradycardia, and wheezing. Level 1+

[95]

Evidence Statement CG66ES151

The RCT comparing carvedilol with metoprolol did not report significant differences between groups in overall safety profile. However, the study stated that no participant taking carvedilol had a respiratory event in contrast with seven events in six participants taking metoprolol. Level 1+

[96]

Evidence Statement CG66ES152

The ASCOT-BPLA study concluded that the most frequent AEs found in the amlodipine based group were peripheral oedema 23%; cough 19%; joint swelling 14%; dizziness 12%; chest pain 8%; fatigue 8%. In the atenolol based group the most frequent AEs were dizziness 16%; fatigue 16%; dyspnoea 9%; cough 8%; erectile dysfunction 7%. Level 1+

[98]

Evidence Statement CG66ES70

Overall, an association could be established between low BP values and a lower incidence of CV events across three of the four studies looking at the relationship between BP levels and CV outcomes.229,232,233,235 However, no clear BP threshold was identified as a potential therapeutic target.

[99]

[100]

[@2004]

[101]

Evidence Statement CG66ES71

An RCT233 with a follow-up of 5 years concluded that intensive BP control (mean BP=280.8/750.3) in normotensive Type 2 diabetes patients was associated with a significantly lower incidence of CV events compared with those in the moderate BP control group (mean BP=1370.7/810.3). Level 1

[@2004]

Evidence Statement CG66ES72

Another RCT conducted in normotensive Type 2 diabetes patients232 showed non-significant differences in the incidence of CV events between the intensive blood control group (mean BP=11810.9/755.7) and the moderate group (mean BP=12410.9/806.5). Level 1+

[100]

Evidence Statement CG66ES73

The analysis completed on the IDNT data229 identified a decreased risk in CV mortality and congestive heart failure (CHF) where the systolic blood pressure

(SBP) decreased from >170 to 120130 mmHg, with a 20 mmHg lower SBP being associated with a 39% reduction in both. An achieved SBP =20 mmHg compared with >120 mmHg showed a greater risk of CV mortality and CHF (see table 12.1). Level 1+

[99]

Evidence Statement CG66ES74

A systematic review234 identified 27 trials which included 33,395 individuals with diabetes and 125,314 without. Overall the analysis suggest that patients with diabetes achieved greater reductions in the risk of total major CV events and CV death with regimens targeting lower BP goals* than those without diabetes (see table 12.2). Level 1+

[102]

Evidence Statement CG66ES75

The observational study235 identified that baseline SBP was lower (14119 mmHg) for those with no complications compared with those who had an MI (15420 mmHg), $p<0.01$. SBP was also lower during the observation period for those with no complications (14516 mmHg) compared with those who had an MI (15215 mmHg), $p<0.05$ and also those who had a stroke (15315 mmHg), $p<0.001$. This study also noted that DBP was lower at baseline for those with no complications (849) compared with those who developed an MI (879 mmHg), $p<0.05$. Level 2+

[101]

Evidence Statement CG66ES76

Five studies228,231233,235 were identified looking at several renal outcomes and their relation with BP control. On the whole, it could be ascertained that high BP levels (SBP and/or DBP) in patients with Type 2 diabetes were associated with a more rapid decline in renal function than in those with lower BP values.

[103]

[104]

[100]

[@2004]

[101]

Evidence Statement CG66ES77

The RENAAL study231 demonstrated that for SBP the baseline level of 160179 mmHg or =180 mmHg compared with less than 130 mmHg had a significantly greater risk of reaching the primary endpoint (time to doubling of serum creatinine, end stage renal disease (ESRD) or death), risk of ESRD or death and risk of ESRD alone. Kaplan-Meier curve also showed that for those with a baseline SBP =140 compared with <140 mmHg there was a significantly higher risk of reaching the primary endpoint and risk of ESRD alone. For achieved SBP those who had a SBP of 140 to =180 mmHg compared with less than 130 mmHg had a significantly greater risk of reaching the primary endpoint; for those with an achieved SBP of 140159 mmHg compared with less than 130 mmHg there was a significantly greater risk of ESRD or death and ESRD alone. For achieved DBP those with a DBP from 90 to =100 mmHg compared with those with an achieved DBP of <70 mmHg had a significantly greater risk of reaching the primary endpoint (time to doubling of serum creatinine, ESRD or death), risk of ESRD or death and risk of ESRD alone231 (see table 12.3.1). Level 1+

[104]

Evidence Statement CG66ES78

The two studies which used intensive and moderate control groups showed significant differences between the groups only for adjusted log urinary albumin excretion rate (UAER) findings.232,233 Level 1+

[100]

[@2004]

Evidence Statement CG66ES79

The further analysis from the IDNT study identified that baseline BP correlated significantly with doubling SCr or ESRD and that 36% of those with baseline SBP >170 mmHg compared with 18% for those with baseline SBP <145 mmHg reached renal endpoint. Following correction for estimated glomerular filtration rate (eGFR) and albumin:creatinine ratio (ACR) each 20 mmHg decrease in SBP was associated with a 30% reduction in the risk of a renal event. Though it should be noted that while there was an increasing risk for reaching a renal endpoint with seated SBP, those with SBP <120 mmHg were not substantially better than those between 120130 mmHg.228 Level 1+

[99]

Evidence Statement CG66ES80

The 10 year observational study identified that baseline SBP and DBP were significantly lower for those with no complications than those who developed renal failure, SBP was also lower for this during the observation period. A BP cut-off of >140 mmHg showed a NSx38.5 increase in the risk of renal failure.235 Level 2+

[101]

Evidence Statement CG66ES81

The intensive (11810.9/755.7) and moderate (12410.9/806.5) groups found NS difference between the groups for progression or regression of retinopathy.232 Level 1+ The other study which considered intensive (1280.8/750.3) and moderate (1370.7/810.3) groups identified less progression of retinopathy with the intensive group compared with the moderate group at both 2 years (13 vs 21%, p=0.046) and 5 years (34 vs 46%, p=0.019).233 Level 1+

[100]

[@2004]

Evidence Statement CG66ES82

The analysis completed on the data from the UKPDS study on retinopathy is detailed in the table 12.4.230 This considered the impact of tight blood pressure control (TBP) aiming for a BP less than 150/85 and less tight blood pressure control (LTBP) aiming for a BP of 180/105 or less. The TBP group had significantly lower microaneurysms, hard exudates and cotton wool spots than the LTBP group. This TBP group also had less retinopathy grading by the Early Treatment of Diabetic Retinopathy Study (ETDRS) grading and lower absolute risk events per 1,000 patient years for photocoagulation and blindness in one eye. Level 1+

[105]

Evidence Statement CG66ES83

The intensive (11810.9/755.7) and moderate (12410.9/806.5) groups found NS difference between the groups for progression or regression of nephropathy.232 Level 1+

[100]

Evidence Statement CG66ES84

The other study which considered intensive (1280.8/750.3) and moderate (1370.7/810.3) groups identified NS difference between the groups for progression of nephropathy.233 Level 1+

[@2004]

Evidence Statement CG66ES85

A systematic review showed that for the outcome stroke, there was no evidence of differences in the effects of the treatment regimens between patients with and without diabetes except in the comparison that included A2RB-based regimens. In this comparison, A2RB provided lesser protection to patients with diabetes compared with those without diabetes (see table 12.5.1).234

[102]

Evidence Statement CG66ES86

For the outcomes coronary heart disease (CHD) and heart failure, the review did not show differences between patients with and without diabetes for any comparison, again except for the comparison that included A2RB. Diabetic patients treated with A2RB experienced a significantly greater protection compared to those without diabetes for the outcome heart failure.234

[102]

Evidence Statement CG66ES87

According to their review, there was also some evidence of a difference between the two patient groups in protection against CV death and total mortality favouring patients with diabetes in the comparison of ACEI-based regimens vs placebo (see table 12.5.1).234

[102]

Evidence Statement CG66ES88

Finally, the review did not report significant differences between different BP lowering regimens (i.e. head-to-head comparisons) in terms of stroke, CHD, heart failure in patients with diabetes. The exception being CCBs, which were associated with a higher risk of heart failure when they were compared with diuretics or beta-blockers,234 (see tables 12.6.112.6.3 for outcomes). In the same

way, no differences were seen in the head-to-head comparisons for total major CV events, CV deaths, and total mortality in patients with diabetes.

[102]

[83]

Evidence Statement CG66ES89

Overall, the evidence appraised showed no significant differences in terms of CV outcomes when treatment with ACEI was compared with other antihypertensive therapies or with placebo. ACEI also failed to demonstrate superiority over other agents on the basis of BP lowering power (unless combination therapy is compared with monotherapy). However, the evidence suggested that treatment with ACEI is related to greater benefits in terms of renal outcomes in patients with Type 2 diabetes as compared with other BP lowering agents.

[76]

[@2005]

[80]

[84]

[78]

[79]

[81]

[@2005]

[77]

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[@2005]

Evidence Statement CG66ES90

The Cochrane review on antihypertensives for preventing diabetic kidney disease found NS difference for ACEI vs placebo (three trials, N=2,683) and for ACEI vs CCBs (six trials, N=1,286).236 These findings were supported by the Cochrane review on ACEI and A2RB for preventing the progression of diabetic kidney disease for ACEI vs placebo (21 trials, N=7,295)* and ACEI vs A2RB (five studies, N=3,409).237 Level 1++

[@2005]

Evidence Statement CG66ES91

The diabetes ALLHAT analysis showed NS difference between the treatments for the incidence of total mortality.247 Level 1+

[84]

Evidence Statement CG66ES92

The extension phase of the HOPE study showed a NS trend towards reduction in major CV events and risk of MI, with ramipril, stroke and CV death as NS. At follow-up of the study and extension there was a significant risk reduction with ramipril for the outcomes of MI, stroke and CV death.241 Level 1+

[80]

Evidence Statement CG66ES93

The diabetes analysis of ALLHAT identified NS difference in the incidence of fatal CHD and non-fatal MI for lisinopril vs chlorthiadone in any of the three glycaemic strata that were analysed diabetes mellitus, impaired fasting glucose and normoglycaemia. This was also evident for diabetes mellitus and normoglycaemia for amlodipine vs chlorthalidone.247 Level 1+

[84]

Evidence Statement CG66ES94

BP reduction with all hypertensive treatments was a consistent feature of the studies and therefore only studies where there were significant differences between the treatments will be highlighted.

[76]

[@2005]

[80]

[84]

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[84]

Evidence Statement CG66ES95

At the 52-week follow-up point, the combination of lisinopril and telmisartan showed significantly greater reductions in both SBP and DBP than the individual monotherapies (p=0.003 for both SBP and DBP).243 Level 1+

[78]

Evidence Statement CG66ES96

Similarly, the combination of amlodipine and fosinopril showed a reduction in sitting BP of 28.7/17.1 compared with 17.2/11.8 (fosinopril, p<0.01) and 19.9/12.8 (amlodipine, p<0.01).245 Level 1+

[79]

Evidence Statement CG66ES97

The study which compared verapamill + trandopril with atenolol + chlorthalidone identified that while both treatments significantly reduced BP that comparison between the groups showed a difference of 4.85 mmHg SBP (1.94 to 7.76, p=0.0011) and 1.79 mmHg DBP (0.26 to 3.32, p=0.0222) favouring atenolol + chlorthalidone.249 Level 1++

[81]

Evidence Statement CG66ES98

A post hoc analysis of the BENEDICT246 study considered the impact on BP control and ACEI therapy on new-onset microalbumuniuria. Baseline SBP, DBP, mean arterial pressure (MAP) and pulse pressure did not predict the onset of microalbuminuria. Participants who developed microalbuminuria had significantly lower reductions in SBP than those who did not develop microalbuminuria (7.911.5 vs 10.611.9, p<0.05). This study also identified that those with followupBP below the medians or with BP reduction above the medians were more frequently on ACEtherapy (particularly trandopirl + verapamil) and less frequently on concomitant treatment withdiuretics, beta-blockers or CCBs.246 Level 1+

[83]

Evidence Statement CG66ES99

The Cochrane review, ACEI and A2RB antagonists for preventing the progression of diabetic kidney disease, identified ACE compared with placebo reduced the

progression from micro- to macroalbuminuria, increased the regression from micro- to normoalbuminuria, and reduced the risk of ESRD.237

[@2005]

Evidence Statement CG66HES09

Ramipril was found to be cost-effective compared to placebo, 2,971/LYG, Beard et al. (2001),263 and 2,486/LYG, Schadlich et al. (2004),264 (1,699/LYG, exchange rate 0.68, 13 March 2007).271

[106]

[107]

Evidence Statement CG66HES10

No statistically significant difference was found between captopril and atenolol. Atenolol had significantly lower mean costs.265

[73]

Evidence Statement CG66HES11

Irbesartan was found to be both more effective and cost saving than amlodipine and standard antihypertensive treatment. Palmer et al. (2004),266 Rodby et al. (2003),267 and Coyle et al. (2004).268

Evidence Statement CG66HES12

Losartan was found to be both more effective and cost saving than standard antihypertensive treatment, Vora et al. (2005).269

[107]

Evidence Statement CG66HES13

Valsartan was found to be both more effective and cost saving compared to amlodipine, Smith et al. (2004).270

[108]

Nearly all people with Type 2 diabetes are at high cardiovascular (CV) risk high enough to justify statin therapy without further assessment.273 Others are at more extreme risk.273 Other therapies in addition to cholesterol-modifying drugs used to ameliorate CV risk include blood glucose lowering, blood pressure

(BP) lowering, and anti-platelet therapies (see recommendations in these areas), together with lifestyle measures. Logically the intensity with which these therapies are used should be determined in part by the level of risk. To a limited extent this can be assessed clinically by summation of presence of risk factors (high waist circumference, low-density lipoprotein cholesterol (LDL-C) level, HbA1c, BP, smoking, family history of premature vascular disease, ethnic group, abnormal serum high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG)) or the presence of particular risk factors (microalbuminuria, previous CV event). However, many of these variables are continuous distributions so it makes sense to ask whether tools are available that make full use of the data which could be made available from their measurement. As diabetes itself is a risk factor, any such approach would have to be diabetes specific. The clinical questions addressed were whether any risk calculator (risk engine) or risk chart, specifically designed for people with diabetes, gave valid and useful assessments of CV risk in people with diabetes, and in what circumstances they might be used.

Discussion

The UKPDS risk engine and to a lesser extent the older JBS-2 charts had some evidence of validity in people with Type 2 diabetes, at least once over the age of 40 years. However, in their latest revision JBS-2 charts for people with Type 2 diabetes are not available. Other estimations based on the Framingham population were not reliable, and the reasons for this were understood. No system included all the desirable variables, with the exception of Archimedes, but this was not intended as a clinical tool. It was noted that a wide range of epidemiological studies suggested that people with diabeteswere over twice as likely as the background population (age and sex matched) to develop CVD, and that many had confounding factors (such as use of antihypertensive or glucose-lowering medications) which prevented use of calculators. Studies such as the UK validation analysis reported above were clearly not consistent epidemiologically with UK populations at diagnosis, and furthermore excluded people already on therapy, and are therefore not reliable as a means of estimating the size of the population justifying therapy except for comparing tools. The group concluded that the normal approach, once age was considered, of managing nearly all people with Type 2 diabetes as having risk >20%/10-years was appropriate, particularly as outcome from MI is known to be worse for those with diabetes, and preventative therapy therefore more cost effective. Particular concerns were also expressed by the GDG over people with microalbuminuria, those with more extreme family histories of CVD, and those with previous and recurrent CV events. This and the age problem meant that it was recognised that any risk estimation had a limited role. However, the GDG were also concerned that some people with Type 2 diabetes do not have the classical phenotype of the disease with abdominal adiposity (or obesity) and low HDL-C. It was concerned that such people should be recognised at diagnosis and managed more conservatively.

When to consider a person to be at high premature cardiovascular risk for age.

Consider a person to be at high premature cardiovascular risk for his or her age unless he or she: is not overweight, tailoring this with an assessment of body-weight-associated risk according to ethnic group is normotensive (< 140/80 mmHg in the absence of antihypertensive therapy) does not have microalbuminuria does not smoke does not have a high-risk lipid profile has no history of cardiovascular disease and has no family history of cardiovascular disease. '

Evidence Statement CG66ES153

One observational study was identified assessing the prognostic value of these two methods in a cohort of patients newly diagnosed with Type 2 diabetes.277 In addition the sensitivity and specificity of both models at a 15%, 10-year CHD risk threshold (NICE guidelines) was compared with that of the ADA lipid threshold (LDL =2.6 mmol/l or TG =4.5 mmol/l). Level 2++

[109]

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[113]

Evidence Statement CG66ES154

At the level of the entire cohort, the number of events predicted by the Framingham equation underestimated both true CVD and CHD events by 33% and 32% respectively, as opposed to the statistically non-significant 13% of CHD events in the case of the UKPDS risk engine. (See tables 13.113.3

[109]

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[111]

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[113]

Evidence Statement CG66ES155

The Framingham results suggested a tendency towards a greater degree of underestimation of CHD events in men than women (41% vs 26%) and for pre-treated rather than untreated BP (42 vs 31%). (See tables 13.113.3.)

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Evidence Statement CG66ES156

When using both risk calculation methods similar proportions were assigned, 10-year scores less than 15% (Framingham 27.3% and UKPDS 25.7%). However, the UKPDS risk engine assigned a 10-year score over 30% to 187 (43.7%) of the study participants as compared with only 88 (20.5%) when derived from Framingham.

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Evidence Statement CG66ES157

The 15%, 10-year CHD risk threshold with both the Framingham and UKPDS risk engines had similar sensitivity for primary CVD as the lipid level threshold 85.7 and 89.8% vs 93.9% (p=0.21 and 0.34) and both had greater specificity 33.0 and 30.3% vs 12.1% ($p<0.001$ and $p<0.001$).

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Evidence Statement CG66ES158

One study275 compared the prognostic value between these two risk calculators by using data from NHS clinical databases. Level 3

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Evidence Statement CG66ES159

Overall, the UKPDS risk engine was found to calculate a significantly higher mean 10-year risk (UKPDS vs JBS, 21.5 vs 18.3%, p<0.0001) with the mean difference of 3.2% (95% CI 2.73.8). However, both methods identified approximately 65% of patients with Type 2 diabetes who would require primary prevention intervention and therefore have comparable accuracy in identifying these high-risk patients.

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Evidence Statement CG66ES160

A bias towards men to have a much higher CHD risk with the UKPDS risk engine was reported. The mean difference in risk score between men and woman was approximately 8.4% with the UKPDS risk engine in comparison with 1.7% with the JBS calculator. For men, the UKPDS risk engine calculated CHD risk approximately 6% higher than the JBS calculator.

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[113]

Evidence Statement CG66ES161

Both methods identified similar proportions of patients with CHD risk of at least 15% over 10 years. However, the main differential feature found between the two methods was the tendency of the UKPDS risk engine to identify significantly more

patients in the high-risk category (>30%) in comparison with JBS (p<0.001). (See table 13.4.)

[109]

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[113]

Evidence Statement CG66ES162

One study276 assessed the prognostic value across four risk calculators. Analysis was conducted by accessing medical records from a cohort of diabetic patients who had attended a NHS clinic for a period of 10 years. Level 3

[109]

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Evidence Statement CG66ES163

Overall, the study showed that all tests (except PROCAM) demonstrated acceptable discrimination with respect to CHD/CVD, however all underestimated the risk of future events

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Evidence Statement CG66ES164

One study278 evaluated these three risk equations in patients with Type 2 diabetes using UKPDS data. Level 3

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[113]

Evidence Statement CG66ES165

The 10-year fatal CVD event rate (95% CI) observed in UKPDS was 7.4% (6.58.3).Framingham underestimated this by 32% with an AR of 5.0%, SCORE overestimated risk by 18% (AR 8.7%) whereas DECODE (AR 6.6%) yielded an acceptable estimate. For males, only SCORE provided a reasonable estimate. In females, only Framinghamperformed well. For Caucasians (N=3,207), the 7.9% (6.79.0) observed event rate was underestimated by 34% using Framingham (AR 5.2%), overestimated by 19% using SCORE (AR 9.4%), and estimated appropriately by DECODE (AR 7.1%)

[109]

[110]

[111]

[112]

[113]

Evidence Statement CG66ES166

The 10-year fatal CHD event rate (95% CI) observed in UKPDS was 6.3% (5.57.1). Framingham underestimated this (AR 4.3%) while SCORE provided a reasonable estimate (AR 5.7%). Both equations provided reliable estimates for females but not males. For Caucasians, the observed rate of 7.2% (6.38.1) was underestimated by both Framingham (4.6%) and SCORE (6.2%).

[109]

[110]

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[112]

[113]

Evidence Statement CG66ES167

A study274 reported results from a total of 74 validation exercises which were conductedinvolving different treatments and outcomes in 18 clinical trials (10 of which were not used to build the model).* Level 3For 71 of the 74 exercises there were no statistically significant differences between the results calculated by the model and the results observed in the trial. Overall, the correlation coefficient for all 74 exercises is r=0.99. If the outcomes in the control group and the absolute differences between the control and treated groups are compared for model and trial, the correlation coefficient is r=0.99. Focusing specifically on the absolute differences in the outcomes, which determines the number neededto treat, the correlation coefficient is r=0.97. For the 10 trials that were not used to build the model, the correlation coefficient is also r=0.99.

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Nearly all people with Type 2 diabetes are at high cardiovascular (CV) risk. Epidemiologicallythat excess risk is independently associated with their hyperglycaemia together with high blood pressure (BP) and dyslipidaemia, the last typically the low high-density lipoprotein cholesterol (HDL-C) and raised triglyceride (TG) levels found as components of the metabolic syndrome.280 Studies have suggested that people with Type 2 diabetes without declared cardiovascular disease (CVD) are at as high a risk of a CVD event as someone without diabetes with declared CVD.273 While this is disputed by other studies, it still leaves individuals with Type 2 diabetes as nearly always in the high CVD risk category, and accordingly it has been usual to manage them actively as if for secondary rather than primary prevention of CVD. Nevertheless, in a few people with Type 2 diabetes the clinical phenotype is not that associated with high CV risk, albeit these people being generally remarkable for not being overweight nor having features of the metabolic syndrome, and being insulin sensitive. More importantly people with Type 2 diabetes who have declared CVD are at much higher risk (>1.5 2.6) of further events or CV death as people with CVD without diabetes.273 Such extreme risk would appear to justify more intensive management than usually offered to someone who has, for example, had a heart attack. The management of CV risk through glucose lowering, BP lowering, and anti-platelet therapy is dealt with elsewhere in this guideline. This chapter deals with lipid-lowering therapy; dietary modification also being dealt with in a separate chapter. Paradoxically, although low-density lipoprotein cholesterol (LDL-C) levels are not particularly raised in people with Type 2 diabetes compared to the background population, the opportunity to lower risk through lipid management is currently greatest through drugs which lower

LDL-C, principally the statins.Nevertheless, a variety of other lipid modifying drugs are available and will be considered in turn.

Discussion

The GDG reviewed the evidence, and their clinical experience of trying to manage the complexities of CV risk in clinical practice. They recognised the primacy of trying to control risk cost effectively against treating-to-target, but also noted the practical utility of measurements in assessing response to therapies and providing motivation to people with diabetes. Ultimately theissue of cost effectiveness could only be resolved in the context of the interventions being used to modify the lipid profile, and the evidence in this area was therefore subsumed into the recommendations on the use of CV risk estimation, statins and fibrates.

When to perform full lipid profile

Perform a full lipid profile (including high-density lipoprotein [HDL] cholesterol and triglyceride estimations) when assessing cardiovascular risk after diagnosis and annually, and before starting lipid-modifying therapy. ’

Evidence Statement CG66ES168

The CTT collaborators meta-analysis identified that there is an approximately linear relationship between the absolute risk reductions in LDL-C found in the 14 studies and the proportional reductions in the incidence of coronary and other major vascular events.281The proportional reductions in major vascular event rates per mmol/l LDL-C reduction were very similar in all subgroups examined (i.e. including the diabetic subgroup), including not just individuals presenting with LDL-C below 2.6 mmol/l (100 mg/dl). Level 1++

[114]

Evidence Statement CG66ES169

The lipid-lowering therapy meta-analysis showed that the RR reductions were similar for both primary and secondary prevention.282 However, the average absolute risk reduction was more than twice as high for those with coronary artery disease (secondary prevention) than for those without it (primary prevention). Primary prevention trials fixed effects analysis due to level of heterogeneity (p=0.18). The pooled RR for CV events with lipid-lowering therapy was 0.78 (0.67 to 0.89), with number needed to be treated (NNT) for benefit of 34.5 (for 4.3 years). Secondary prevention analysis random effects analysis as there was substantial between study heterogeneity (p=0.03). The pooled RR for CV events

with lipid-lowering therapy was similar to that for primary prevention 0.76 (0.59 to 0.93), with NNT for benefit for of 13.8 (for 4.9 years). The authors concluded that target cholesterol levels and the effectiveness of dose titration (or the use of multiple agents) have not been rigorously examined. Most studies compared a lipid lowering drug with placebo but did not evaluate the effect of reaching specific cholesterol levels. Level 1++

[115]

Evidence Statement CG66ES170

One RCT291 found that over the 5 years of double-blind treatment, the incidence of a major CV event* was significantly lower in patients receiving atorvastatin 80 mg than in those receiving atorvastatin 10 mg. This represented a 25% reduction in the risk of major CV events in favour of the high-dose group ($p>0.026$). This trend was observed across all quintiles of patient age and duration of diabetes and in patients with HbA1c =7% and A1C >7%. Level 1++

[116]

Evidence Statement CG66ES171

The same RCT291 reported significant differences between the groups, in favour of atorvastatin 80 mg, for the secondary outcomes of time to cerebrovascular event ($p<0.037$) and time to CV event ($p<0.044$). Level 1++

[116]

Evidence Statement CG66ES172

A post hoc analysis of the ASCOT-LLA study290 found a significantly lower incidence of CV events in the subpopulation of people with Type 2 diabetes treated with atorvastatin 10 mg when compared with those receiving placebo. (Hazard ratio 0.77, 95% CI 0.61 to 0.98, $p<0.036$.) Level 1+

[117]

Evidence Statement CG66ES173

A post hoc analysis of the DALI trial286 showed that both standard and aggressive therapy with atorvastatin (1080 mg) did not reverse endothelial dysfunction (as measure by the surrogate marker of flow mediated vasodilatation). Level 1+

[118]

Evidence Statement CG66ES174

A post hoc analysis of the CARDS trial289 analysed the time between initiation of atorvastatin 10 mg and the appearance of significant differences in the incidence of CV events when compared to placebo. The study demonstrated that by 1 year of follow-up the estimate of the treatment effect of atorvastatin 10 mg on the primary endpoint of major CV events was already at its final values of 37% reduction, and by 18 months the CI did not include unity. Level 1++

[119]

Evidence Statement CG66ES175

An RCT291 reported that end-of-treatment LDL-C levels increased by 3% to a mean of 98.6 mg/dl (2.5 mmol/l) in patients who continued atorvastatin 10 mg, while a further reduction of 19% to a mean of 77.0 mg/dl (2.0 mmol/l) was observed in those assigned to atorvastatin 80 mg ($p < 0.0001$). Level 1++

[116]

Evidence Statement CG66ES176

The same study291 reported significant differences between the groups, in favour of atorvastatin 80 mg, for total cholesterol (TC) levels and TG. Level 1++

[116]

Evidence Statement CG66ES177

One RCT 287 reported that simvastatin 80 mg treatment resulted in significantly lower low-density lipoprotein n (LDL) levels compared with simvastatin 40 mg g ($p<0.001$). Level 1+

[120]

Evidence Statement CG66ES178

The same study287 showed that after a 6-week treatment, approximately 87% of patients treated with simvastatin 80 mg, and 82% of patients treated with simvastatin 40 mg, had LDL values that met or exceeded the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) treatment goal of <100 mg/dl (2.6 mmol/l), compared with only 14.3 of patients treated with placebo. No statistical significance was reported. Level 1+

[120]

Evidence Statement CG66ES179

An RCT288 comparing treatment with rosuvastatin 10 mg vs atorvastatin 10 mg, reported that at the end of the study rosuvastatin-treated patients had significantly lower LDL levels compared with the atorvastatin group ($p<0.0001$). The study also reported that at 16 weeks, significantly more patients achieved their LDL goal with rosuvastatin compared with atorvastatin (94% vs 88%, $p<0.05$). Level 1+

[121]

Evidence Statement CG66ES180

The ASCOT-LLA post hoc study290 found that among diabetic participants in the atorvastatin group, TC and LDL levels at year one of follow-up were lower than in the placebo group by ~1.3 and 1.2 mmol/l respectively. By the end of the study, these differences were 0.9 and 0.9 mmol/l respectively. However, no statistical analysis was performed. Level 1+

[117]

Evidence Statement CG66ES181

In relation to lipid levels, the DALI post hoc analysis found that after 30 weeks, patients receiving atorvastatin 80 mg had significantly lower LDL levels than those treated with only 10 mg of atorvastatin ($p<0.01$)

[118]

Evidence Statement CG66ES182

An RCT291 found no significant differences between the treatment groups (atorvastatin 10 mg and 80 mg) in the rate of treatment related adverse events (AEs), including myalgia, or persistent elevations in liver enzymes. No incidents of rhabdomyolysis were reported in either treatment group. Level 1++

[116]

Evidence Statement CG66ES183

One RCT287 comparing different doses of simvastatin (simvastatin 40 and 80 mg) concluded that no drug related serious clinical AEs were observed in the treatment groups. However, the study reported that two patients on simvastatin 80 mg treatment had an Alanine Transaminase (ALT) and Asparte Transaminase (AST) level >3 times the upper limit of normal; one of these patients was discontinued

because of these elevations (the liver function tests returned to normal after discontinuation of the therapy). Level 1+

[120]

Evidence Statement CG66ES184

An RCT288 comparing treatment with rosuvastatin 10 mg vs atorvastatin 10 mg, reported that both treatments were well tolerated, with overall incidences of AEs being similar between the groups. According to the study ten patients discontinued because of AEs, three in the rosuvastatin group and seven in the atorvastatin group. There were no cases of myopathy. Level 1+

[121]

Evidence Statement CG66ES185

The ASCOT-LLA post hoc study290 found that the use of atorvastatin in the diabetic population was not associated with any excess risk of adverse reactions, and there were no significant differences in liver enzyme abnormalities between those allocated statin and placebo. No cases of rhabdomyolysis were reported. Level 1+

[117]

Evidence Statement CG66ES186

The double-blind, multicentre FIELD study with N=9,795 participants compared fenofibrate 200 mg/day with a placebo in a Type 2 diabetes population, over a 5-year duration. At 4 months, 1 year, 2 years and at completion of the study there were significant decreases in TC, LDL-C and TG levels and increases in HDL-C levels with fenofibrate compared with placebo. For study participants who started other lipid-lowering therapy during the study (total N=2,720, N=944 placebo group and N=1,776 fenofibrate group) they showed smaller changes in lipid levels, but the significance between the groups remained $p<0.05$ at 2 years. At study close the changes remained significant for TC and TGs between the groups; however, the changes in LDL-C and HDL-C were NS. There were small percentages (0.5 with placebo and 0.8% with fenofibrate) of possible serious adverse drug reactions. Four participants had rhabdomyolysis which fully resolved (N=3 with fenofibrate and N=1 with placebo). Rates of new cancer diagnosis were similar between groups.GI events were the most frequently reported event, these were noted with N=975 (20%) of the fenofibrate and N=927 (19%) of the placebo group. Level 1++

[122]

Evidence Statement CG66ES187

This single centre, double-blind study compared fenofibrate 160 mg/day with simvastatin 20 mg/day and both monotherapies with the combination of fenofibrate and simvastatin, with N=300 participants.298 Fenofibrate was found to have significantly greater reductions in TC and for LDL-C than simvastatin and than the combination of the drugs, differences between simvastatin and the combined group were NS. The fenofibrate and combined groups had significantly higher decreases in TGs than simvastatin (NS between fenofibrate and combined treatments). Adverse events There were no serious drug related AEs. Level 1++

[123]

Evidence Statement CG66ES188

This study compared fenofibrate 200 mg/day and atorvastatin 20 mg/day monotherapiescompared with the combination of fenofibrate and atorvastatin, with N=120 participants.296 Treatment goals The treatment goals for LDL-C (2.4 mmol/l), TGs (2.6 mmol/l) and HDL-C (1.2 mmol/l) were reached in significantly more (reached by 97.5%, 100% and 60% respectively, $p<0.05$) participants for the combination of fenofibrate and atorvastatin than the monotherapies. The fenofibrate group compared with the atorvastatin group reached the treatment goals in a significantly higher percentage for HDL-C (30% vs 17.5%) and TGs (92.5% vs 75%), while the reverse was true for LDL-C with 80% of the atorvatstatin reaching the treatment goal compared with 5% of the fenofibrate group. Lipids The combination treatment reduced the TC, TGs and LDL-C significantly more than the atorvastatin or the fenofibrate as monotherapies. This combination also significantly increased HDL-C compared with atorvastatin monotherapy but not compared with fenofibrate. Adverse events There were no significant AEs reported in this study. Level 1+

[124]

Evidence Statement CG66ES189

This double-blind study over 12 months compared the combination of extended-release fluvastatin 80 mg and fenofibrate 200 mg and the monotherapy of fenofibrate 20 mg, N=48 participants.295 At 6 months the combination showed a significantly higher reduction in LDL-C compared with fenofibrate monotherapy. For the 12-month point significantly there were greater reductions in LDL-C and TG levels and increases in HDL-C with the combination group compared with the monotherap. Adverse events No serious AEs were reported, N=3 discontinued in the study due to myalgia. Level 1++

[125]

Evidence Statement CG66ES190

This multicentre study incorporated both a double-blind, fixed-dose phase and an open-label titrating dose phase, N=216.297 Fixed dose: the 6-week fixed-dose phase had placebo, rosuvastatin 5 mg and rosuvastatin 10 mg groups. There were significant decreases for both rosuvastatin 5 mg and 10 mg groups compared with increases with placebo in TC (36.6%, 31.4% vs 1.1%, p<0.001) and TGs (24.5%, 29.5% vs 4.7%, p<0.001) and compared with decreases in LDL-C levels with placebo (40.7%, 45.8% vs 0.6%, p<0.001). At week 6, 77.4% of those in the rosuvastatin 10 mg group had reached the LDL-C goal of <100 mg/dl, compared with 8.3% of those receiving placebo. This multicentre study incorporated both a double-blind, fixed-dose phase and an open-label titrating dose phase, N=216.297 Fixed dose: the 6-week fixed-dose phase had placebo, rosuvastatin 5 mg and rosuvastatin 10 mg groups. There were significant decreases for both rosuvastatin 5 mg and 10 mg groups compared with increases with placebo in TC (36.6%, 31.4% vs 1.1%, p<0.001) and TGs (24.5%, 29.5% vs 4.7%, p<0.001) and compared with decreases in LDL-C levels with placebo (40.7%, 45.8%vs 0.6%, p<0.001). At week 6, 77.4% of those in the rosuvastatin 10 mg group had reached the LDL-C goal of <100 mg/dl, compared with 8.3% of those receiving placebo. Adverse events The most frequently reported AEs in a small number of participants were GI related, myalgia and increases in ALT and creatine kinase (CK) levels. Level 1+

[126]

Evidence Statement CG66ES191

This study compared gemfibrozil 1,200 mg and a matched placebo in the Veterans Affairs High Density Lipoprotein Intervention Trial (VA-HIT) and included a subgroup diabetic, N=627.299 This study considered major CV events and identified in the diabetes group a significant reduction in the risk of major CV events of 32%, of CHD death 41%, and of stroke 40%, compared with placebo. The lipid level analysis was not analysed by diabetic subgroup. Level 1+

[127]

Evidence Statement CG66ES192

This study compared gemfibrozil 1,200 mg compared with simvastatin 20 mg, N=70.300 This study did not complete comparisons between the groups, both treatments significantly decreased TC and TG levels, and increased HDL-C compared with the baseline. There were significant decreases in LDL-C with simvastatin compared with baseline but not with gemfibrozil. There were small numbers of incidents of GI events with gemfibrozil and generalised weakness and muscle pain with simvastatin. Level 1+

[1]

Evidence Statement CG66ES193

This double-blind, multicentre study with N=268 participants compared gemfibrozil 1,200 mg and pravastatin matched placebo with pravastatin 40 mg and gemfibrozil matched placebo. Lipids There were significantly greater reductions in TC and LDL-C with pravastatin than with gemfibrozil. Conversely there was a significantly greater reduction in TG levels with gemfibrozil than with pravastatin p<0.001. Changes in HDL-C were NS between the groups. Adverse events The AEs reported were considered not severe and the most frequent were GI related (N=28 gemfibrozil and N=24 pravastatin). Level 1++

[2]

Evidence Statement CG66ES194

This open-label, crossover study compared gemfibrozil and atorvastatin and a combination of both drugs, in a titrating dose study, N=44.302 Lipids The atorvastatin and combination groups had significantly greater reductions in LDL-C than the gemfibrozil group (reductions NS for atorvastatin vs combination). For TG levels the gemfibrozil and combination groups had significantly greater reductions than the atorvastatin group (reductions NS for gemfibrozil vs combination). There were NS differences between the monotherapies and the combination treatment for HDL-C levels. Adverse events GI related (abdominal discomfort, constipation, loose stools, nausea) were reported by N=6 (atorvastatin), N=11 (gemfibrozil) and N=8 (combination). Level 1+

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