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Introduction

The management of cardiovascular risk is a huge area for debate, involving a multitude of factors, disciplines and guidelines.

The *Cardiodiabetes Forum*, sponsored by MSD Ltd and Schering-Plough Ltd, was a multidisciplinary meeting of diabetologists, cardiologists, and clinicians with particular interest in lipid and cardiovascular disease management who came together at the Royal College of Physicians in London to discuss some of the current hot topics in cardiovascular risk management in a series of five 'round table' style debates. Each debate was led by a member of the faculty; areas for consideration included the translation of cholesterol guidelines into practice, the use of new and existing surrogate markers, the management of risk in 'at-risk' populations and the need for a more collaborative approach in the management of diabetic patients with cardiovascular disease. Each group had a series of questions to address to give the debate some structure, but the content and areas discussed were largely dictated by the participants.

The subject matter of these debates has become even more topical recently with publication of the National Institute for Health and Clinical Excellence (NICE) Guidelines on the Management of Type 2 Diabetes[1] and Lipid Modification.[2]

The consensus reached at the meeting is broadly in line with these guidelines. In particular, NICE recommends the use of lipid-lowering therapy in type 2 diabetic patients over the age of 40 with normal to high cardiovascular risk (or under 40 with a poor cardiovascular risk profile), aiming for a total cholesterol level below 4.0 mmol/L or low-density lipoprotein cholesterol (LDL-C) level below 2.0 mmol/L.[1] Lipid-lowering therapy for primary prevention of cardiovascular disease (CVD) in non-diabetics is recommended for adults who have a 20% or greater 10-year risk of developing CVD, although there is no target level for total or LDL cholesterol. Targets are recommended for secondary prevention patients and it is suggested that an 'audit' level of total cholesterol of 5.0 mmol/L is used since fewer than half will achieve total cholesterol below 4.0 mmol/L or LDL-C below 2.0 mmol/L.[2]

The main points from each debate, plus consideration of the wider implications for practice, are summarised within this supplement

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Translating cholesterol guidelines for the treatment of patients at high risk of cardiovascular disease into practice

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Current guidelines for primary and secondary prevention of CVD

Current guidelines for primary and secondary prevention were the subject of this Group's debate during the forum. An important cause for concern identified during this discussion was that no single, unified set of multidisciplinary guidelines is used by hospitals, primary care trusts (PCTs), networks, regions and strategic health authorities. Individual hospitals or PCTs use a range of guidelines and cholesterol targets (see **table 1**).[1–3] The participants – all hospital consultants – reported that they would like to be able to select the lipid targets and treatment according to the needs of each patient.

New guidelines: what's important?

Patient groups

The discussants considered that any new, standardised local guideline should encompass both primary and secondary prevention for patients with established cardiovascular disease (CVD) and 'secondary prevention equivalents'. Current guidelines concur on the value of secondary prevention in patients with CVD – defined as coronary heart disease (CHD), transient ischaemic attack (TIA)/ stroke or peripheral arterial disease (PAD) – but concern was expressed during the debate that, although these differing presentations are manifestations of the same disease process, intervention may be less aggressive in some groups of patients, such as those with PAD.

Discussants recommended that:

- Primary prevention should be directed towards people with an estimated 10-year risk of CVD ≥ 20% according to Joint British Societies' (JBS 2) risk calculation charts[1]
- Intervention should be focused particularly on people with type 2 diabetes or hypertension since it may be impractical to identify all eligible patients within the general population
- Identification and treatment should be the responsibility of primary care since these patients can be readily identified through Quality and Outcomes Framework (QOF) registers
- If a 10-year 20% CVD risk were the only criterion, almost everyone aged over 65 would be eligible for primary prevention. This makes it essential to take into account biological age, life expectancy and the presence of co-morbidities and other cardiovascular (CV) risk factors when considering primary prevention in older patients.

'For primary prevention, intervention should be focused particularly on people with type 2 diabetes or hypertension'

Secondary prevention 'equivalents' are patients with type 2 diabetes, some hypertensive patients and some with chronic kidney disease (CKD). The Group recommended that all diabetes patients aged 40 years and above should receive lipid-lowering therapy, regardless of their cholesterol levels. Hypertensive patients, however, should only receive treatment after an overall risk assessment that aims to identify patients who have a 20% or greater 10-year risk of developing CVD.[4] Similarly, while some CKD subgroups, such as diabetic patients, should be considered for treatment if thought to be at higher risk[5], there is, as yet, no consensus within the renal community on the management of other patient subgroups, such as those with glomerulonephritis. The Group noted that clarification

on the role of lipid-lowering therapy in CKD is expected from the National Institute for Health and Clinical Excellence (NICE) later in 2008.

Guideline compilation

The ultimate aim in guideline compilation should be to avoid local inconsistencies and to ensure consistent practice across the region. Guidelines are most appropriately compiled by an expert multidisciplinary team that includes specialists in lipidology, biochemistry, pharmacy, pharmacology, cardiology and diabetology to help ensure secondary care acceptance, but the Group emphasised the importance of involving both medical and pharmacy representatives from primary care.

The development of guidelines should consider the current evidence base, choice of treatment, economic issues, and QOF and/or NICE targets, while drawing on best practice outlined in existing local or national guidelines. Concern was expressed about the challenge presented by the perceived conflict of interest between best clinical practice and economic realities. The Group concluded that the balance between these sometimes competing values can only be achieved through consensus discussion involving stakeholders from primary care, secondary care, PCT management and pharmacy.

'All diabetes patients aged 40 and over should receive lipid-lowering therapy, regardless of cholesterol levels'

An example guideline

To better understand the process of compilation, an example guideline looking at the primary or secondary prevention of established CHD was discussed. While it was agreed that reducing low-density lipoprotein (LDL) cholesterol is increasingly accepted as being equivalent to reducing risk, it was emphasised that the underlying aim of treatment is to address each patient's CVD risk, not to treat the biochemistry. The Group agreed that there is general agreement among clinicians that the initial step in this instance should be to prescribe generic simvastatin 40 mg daily but there was less consensus about what steps to take if, for example, a patient does not achieve target cholesterol, is intolerant of treatment, or if a statin is contra-indicated. Consequently, a guideline must focus on subsequent steps in the treatment algorithm.

Industry and charity sponsored nurses could drive guideline implementation

Implementing new guidelines

Identify a clinical champion

If implementation is not driven by a PCT, the Group agreed that a clinical lead or champion is invaluable – someone who can take local responsibility, by convening other disciplines or by driving implementation. This person must have credibility to both primary and secondary care - an ideal candidate would be a clinical pharmacologist, as they are seen as non-partisan and able to promote guidelines across medical disciplines. Since many areas do not have a clinical pharmacologist, in practice a clinical champion is likely to be a member of the multidisciplinary clinical team working in close co-operation with pharmacy.

Monitor adherence

Monitoring adherence to guideline standards and targets is crucial, and the Group recommended that the strategic health authority or network should be responsible for monitoring implementation across a large geographical area. In primary care, QOF targets help to support adherence to and implementation of guidelines, but there is no equivalent incentive in secondary care apart from a physician's desire to maintain professional and clinical standards (which also applies in primary care). The Group thought that detailed discussion of the issue was outside its remit, but recommended that relevant professional organisations might explore the potential role of incentivisation to support guideline implementation in secondary care.

Table 1. Current cholesterol guidelines for high-risk cardiovascular disease (CVD) patients

- Joint British Societies' (JBS 2):[1] optimal targets of total cholesterol (TC) < 4.0 mmol/L and low-density lipoprotein cholesterol (LDL-C) < 2.0 mmol/L, or 25% reduction in TC and 30% reduction in LDL-C, whichever achieves the lower absolute value
- National Service Framework for Coronary Heart Disease (NSF for CHD):[2] TC < 5.0 mmol/L and LDL-C < 3.0 mmol/L, or 30% reduction, whichever is greater
- Local primary care trust (PCT) guidelines: driven by the NSF targets and Quality and Outcomes Framework (QOF)[3] target of TC ≤ 5.0 mmol/L
- Local laboratory practice, highlighting TC > 5.0 mmol/L and LDL-C > 3.0 mmol/L in biochemistry reports
- National Institute for Health and Clinical Excellence (NICE) Lipid Modification Clinical Guideline.[8] No targets for primary prevention. Use 'audit' concentration of total cholesterol of 5.0 mmol/L for secondary prevention since more than half of patients will not achieve TC < 4.0 mmol/L and LDL-C < 2.0 mmol/L
- NICE Type 2 Diabetes Clinical Guideline.[9] TC < 4.0 mmol/L and LDL-C < 2.0 mmol/L

Major obstructions to progress

The main barrier to moving forward with guidelines identified by the Group was lack of professional ownership; conversely, if stakeholders feel strongly that they own the

Discussion

Q: ***There appears to be no unified guideline on prevention across primary and secondary care. Is this a common experience?***

A: PCTs are also looking carefully at the NICE guidelines on secondary prevention following myocardial infarction (MI).[6] JBS 2 was confounded by the statement[7] by the National Director for Heart Disease & Stroke that national targets are TC < 5.0 mmol/L and LDL-C < 3.0 mmol/L rather than, respectively, < 4.0 mmol/L and < 2.0 mmol/L. The situation will hopefully be clarified by the publication of the NICE guidelines on lipid modification.[8]

Q: ***Guidelines are important in educating doctors, but should treatment not depend on the doctor's judgement of the needs of the patient?***

A: Guidelines are designed for the vast majority of patients but should not restrict clinicians' freedom to treat an individual patient's exceptional needs. The issue is how to define the exceptions.

Q: ***The tracking or monitoring of guidelines is an important issue, isn't it? Clinicians must have flexibility and non-clinicians should understand that a simple tick-box approach to targets is inappropriate. The people with whom we work, especially managers, also need to be aware that guidelines are not fixed and must be revised regularly according to evolving evidence.***

A: Agreed.

guidelines, they are more likely to drive implementation. The division of labour in guideline implementation must also be taken into account: while secondary care may set the targets or design the algorithms, delivery will predominantly take place in primary care within the limits of evidence, safety, tolerability and economics.

Facilitating guideline implementation

Education

Education, the Group felt, is the key to any guideline implementation-- to include education of physicians in primary and secondary care, not only on general issues of implementation but also on specific areas where there is currently a lack of clarity.

'The potential conflict of interest between best clinical practice and economic reality needs to be addressed by consensus discussion'

Individualised and general public health education is also essential. The Group recognised the benefit for patients of 'knowing their numbers', as well as the value of patient-held records, which can be used during a consultation to motivate patients to continue to adhere to treatment while noting that cholesterol is a health issue that should be addressed throughout the population at high CVD risk.

Support posts

Local/regional risk factor or cardiovascular nurses can facilitate implementation by working within the community while still accountable to secondary care. Such nurses should be responsible for education, follow-up, drug titration, and monitoring of adherence and complications and not focus on a single aspect of management such as drug therapy.
The Group suggested that, based on the model of Parkinson's disease nurse specialists, these support posts could initially be supported by industry and/or charities but that ultimately funding should be taken over by the Department of Health.

Drug pricing

Industry could also help to facilitate guideline implementation by reducing the cost of drugs and possibly by introducing a flat pricing structure for all doses of lipid-lowering therapy. The Group considered that the latter would be particularly relevant if biochemical targets were in future reduced to total cholesterol (TC) < 4.0 mmol/L and LDL-cholesterol < 2.0 mmol/L

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The use of surrogate end points in cardiovascular disease and diabetes

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Introduction

What is a surrogate end point?

Research, particularly intervention trials, can only be appropriately interpreted with pre-defined end points. The hypothesis being tested will be either proven or disproven by comparing the occurrence of the defined end points in the intervention and comparator groups. 'Hard' clinical end points are definable, identifiable and clinically important outcomes that directly reflect states of health, disease and illness.

A 'surrogate marker' can be used in place of a hard clinical end point. It is assumed to be representative of the ultimate clinical end point goal - an increased incidence of the surrogate marker will necessarily be followed by an increased frequency of the hard end point. In some cases, the surrogate marker is an intermediate step in the direction of the hard end point, being linked through pathophysiological processes, while in others it merely identifies a person at increased risk of the hard end point.

A surrogate marker is measurable, recordable and often changes more rapidly and more sensitively than the hard end point in response to interventions. To be useful, the surrogate marker must be affected by the study intervention. Usually several surrogate markers are pre-defined in clinical trials as primary and secondary end points. Because surrogate end points tend to occur earlier and more often than 'hard' end points, power calculations in interventional studies are often based upon expected numbers of surrogate end points, and these become the primary end points of the study.

Use of surrogate markers

Surrogate markers are important for the research, development and registration of new drugs, for example in evaluating drug dose-response and optimal doses, determining clinically relevant efficacy, toxicity and the safety/tolerability profile.

Surrogate markers can be used in different ways:

- as an aid to diagnosis
- as a tool for staging disease
- as an indicator of disease status
- as a measure to predict and/or monitor clinical response to an intervention.

Surrogate markers are generally more cost-effective or more easily measured than hard clinical end points.

Clinical research and practice

Discussants considered a number of specific surrogate markers for cardiovascular disease and diabetes in the field of clinical research. Left ventricular hypertrophy (LVH), for example, as measured using ECG is an indicator of severity of hypertension. Regression of LVH may be used to estimate the efficacy of antihypertensive agents, while LVH itself is used as an indicator of risk for stroke.

'Surrogate markers represent intermediate steps to a hard end point or to identify individuals who are at risk'

Cholesterol reduction is used as a surrogate marker of one factor in reducing risk of coronary artery disease and cardiovascular mortality. Intravascular ultrasound (IVUS) was used to measure changes in atheroma burden as a surrogate marker for cardiovascular events in the REVERSing Atherosclerosis with aggressive Lipid-lowering therapy trial (REVERSAL).[1]

Discussion

Q: ***Are surrogate markers a good thing?***

A: Yes, but they do need to be validated, particularly when used to assess a new class of therapies.

Q: ***Can surrogate end points make a useful protocol for primary care?***

A: Yes. For example, in diabetic retinopathy screening photographs of the eye are already used to assess disease progression.

Both blood pressure and urinary albumin excretion may be used as surrogate markers for cardiovascular disease in patients with hypertension and type 2 diabetes, as in the Candesartan And Lisinopril Microalbuminuria (CALM) trial,[2] for instance. Changes in glycosylated haemoglobin (HbA_{1c}) are used as a surrogate marker for microvascular complications in diabetes.

'They are used extensively in clinical trials and clinical practice, and can be used to drive national audits and to monitor performance'

Numerous laboratory parameters are routinely used as surrogate markers in clinical practice (see **table 1**).

Performance management strategies

Surrogate measures are also important in practice as they can be used to drive national audits, and they are assessed in the Quality and Outcomes Framework (QOF).[3] Key QOF targets for general practitioners involve measurement and recording of parameters to manage coronary heart disease, hypertension and diabetes, among many other conditions. Waiting times, average length of hospital stay and readmission rates are also often used as markers of quality of care.

Myocardial Ischaemia National Audit Project (MINAP) guidelines/targets, such as door-to-needle time and call-to-needle time, are used as measures of earlier treatments and surrogates for better outcomes. The proportion of patients discharged from hospital who are taking aspirin, statins and other treatments may be used as surrogate markers of lower recurrence of events.[4]

Validation of surrogate end points

In order to assess/validate the usefulness of a surrogate marker in determining the effectiveness of a particular treatment, the Group recommended that various parameters should be determined (**figure 1**).

Ideally, the surrogate marker should be easier to measure, show more rapid results and be more cost-effective to measure than a hard end point. It should also have low inter-observer variability and should be reliable with repeated measures, especially in chronic diseases.

Other clinical surrogate markers

Some surrogate markers have ultimately been shown to be unrelated to the clinically meaningful end point or, despite an association, to have limited clinical value. The Group identified these as:

- Ventricular ectopic activity, as measured by ventricular premature beats. This was used as a surrogate marker for sudden death in post-myocardial infarction patients in the Cardiac Arrhythmia Suppression Trial (CAST). The trial demonstrated a decrease in ventricular ectopic activity but mortality rates increased in both treatment groups.[5]
- Microalbuminuria and proteinuria, although surrogate end points for target organ damage due to hypertension,[6,7] were felt by the Group to be of limited practical value.
- High-sensitivity C-reactive protein is a surrogate marker for inflammation but it is not generally used in clinical practice[8]

Figure 1. Suggested pathway for validating a surrogate marker

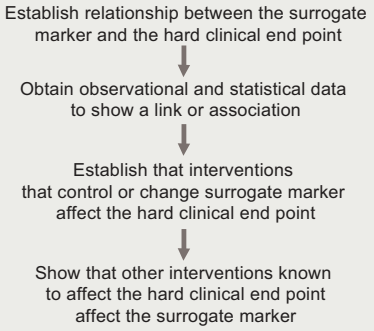

Table 1. Examples of surrogate markers

Cardiovascular disease
- blood pressure
- waist circumference
- total cholesterol and low-density lipoprotein (LDL)-cholesterol
- smoking

Diabetes control and complications
- plasma glucose
- HbA1c
- photography of the retina

Heart failure morbidity and mortality
- Brain natriuretic peptide (BNP) levels

Other
- CD4+ counts and viral loads (for AIDS events and survival)
- bone mineral density (for future risk of fracture in osteoporosis)
- C-reactive protein (as a marker of an inflammatory process)

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DISCUSSION THREE

Cardiodiabetes – is a joint approach the way forward?

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Introduction

Diabetes is a known, independent, risk factor for cardiovascular disease and since diabetes and serious cardiovascular disease are frequently observed together, the term 'cardiodiabetes' is increasingly applied to describe the convergence of these conditions. The European Society of Cardiology – European Association for the Study of Diabetes (ESC-EASD) Task Force guidelines of 2007 acknowledge the inter-relationship between diabetes and cardiovascular disease and call for an early, multidisciplinary approach to the recognition and intensive management of all cardiodiabetes risk factors.[1] The evidence that diabetes is a key factor in cardiovascular disease is also highlighted by the National Institute for Health and Clinical Excellence (NICE) clinical guidelines on lipid modification and type 2 diabetes, which recommend treatment of serum lipids in patients with type 2 diabetes mellitus and those with established cardiovascular disease (CVD).[2,3]

'Prevention of cardiovascular disease must focus equally on patients with established atherosclerotic disease and on people with diabetes'

Traditionally, cardiologists and diabetologists have played parallel roles in managing cardiovascular risks in their patient populations. The emergence of cardiodiabetes as a term poses a number of questions with implications for optimal and effective, collaborative management of patients in the UK.

The Group set out to summarise current consensus on the appropriateness of the term cardiodiabetes, and to consider the practicalities, in the UK, of adopting a revised approach to patient care that successfully bridges specialist disciplinary divides while supporting healthcare for the individual based in primary care.

Table 1. Cardiodiabetes – what's in a name?

The fusion of the prefix cardio with the suffix diabetes:

- Reminds diabetologists to assess blood pressure, lipids, weight and glucose management
- Prompts cardiologists to consider diabetes-related risk factors in patient assessment and management
- The combination of cardio with diabetes tells patients more about their condition

Is the term cardiodiabetes really meaningful?

A number of terms are used to describe the convergence of cardiovascular disease and type 2 diabetes in a patient. While there is an increasingly prevalent view that diabetes should be viewed from the outset as a vascular disease, the consensus view of the Group was that use of hybrid terms to acknowledge the concurrent diseases and risks at play is useful for both clinicians and for patients.

The term cardiodiabetes was preferred by the Group over the word 'cardiobetes', which was considered too truncated a term. In recognition that many patients with diabetes and cardiovascular disease may be obese, 'cardiodiabesity' was suggested as an appropriate catch-all term. Further, the high risk for renal complications in patients with convergent diabetes and cardiovascular disease led to the suggestion of 'cardiorenaldiabetes' as another descriptor.

'The term 'cardiodiabetes' is a useful reminder for clinicians to assess multiple risk factors'

The term of cardiodiabetes was viewed as most useful for clinicians **(table 1)**, serving to

remind diabetologists of the need to assess blood pressure and lipid parameters in addition to weight and glucose management, and similarly serving to prompt cardiologists to consider diabetes-related risk factors in patient assessment and management. For patients too, the combined term is meaningful, and the addition of the 'cardio' prefix to diabetes adds impact to the overall descriptor.

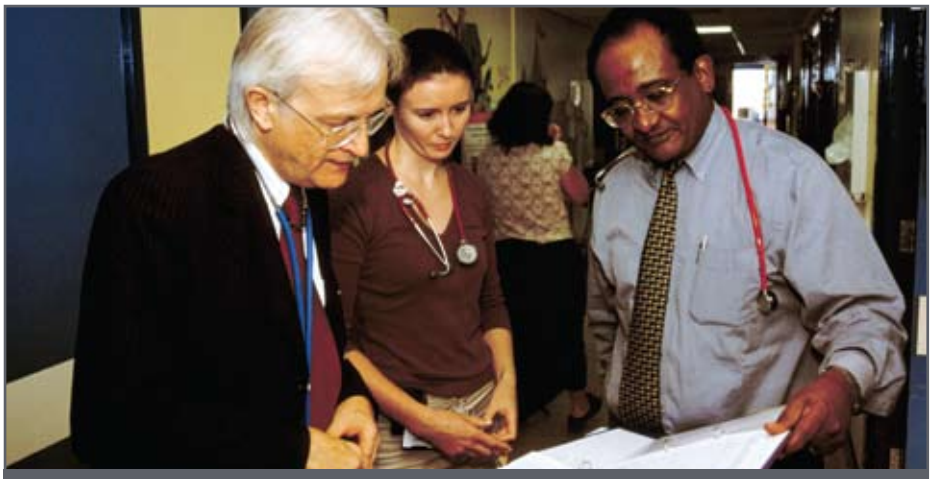
The rising tide of global obesity was recognised by the Group to be a major driver of diabetes and a contributor to the burden of cardiovascular disease. While the term metabolic syndrome is useful for prompting consideration of the aetiology of a host of risk factors that may collectively increase a patient's cardiovascular risk profile,[4] the Group considered that this term has a different application to the term cardiodiabetes. The metabolic syndrome may be more useful when considering prevention of the continuum from obesity through diabetes to cardiovascular disease, whereas the term cardiodiabetes is more applicable to the particular spectrum of cardiovascular disease, plus more diffuse peripheral vascular and renal disease, that is associated with diabetes.

'Physicians must communicate and collaborate to combine the best of specialist experience with primary care expertise'

The practicalities of collaborative management of two separate risks

Cardiodiabetes is a useful term to describe a particular group of patients but leads to the question of who should manage such patients - one particular speciality, or a care team in which the primary care physician plays the key role?

The Group felt that diabetologists, cardiologists, lipidologists and renal physicians all have experience and knowledge that must be included and shared as part of patient management. Diverse approaches to patient management which span both primary and secondary care are employed currently in the UK. A patient may be seen by both diabetes and cardiology specialists (arguably with some duplication of assessments, advice and consultation costs) or, more rarely, may be seen at joint specialist clinics run at hospital centres, or may be managed through Primary Care Trust (PCT) one-stop clinics.



Experience and knowledge should be shared as part of patient management

Supporting primary care

There is no single model for the provision of care services to patients who fit the cardiodiabetes description and no real consensus on whether the care of such patients needs the creation of a cardiodiabetes specialist or specialist team. Rather than developing a new speciality, more could be done to encourage experience sharing between specialities, and to support GPs with a special interest (GPwSI) in diabetes and cardiovascular disease.

Communication and experience sharing are also essential to prevent hospitals becoming the place of last resort in disease management and to ensure that patients have early and appropriate access to clinical expertise that could affect the direction of disease management and, ultimately, prognosis and outcome.

While there is scope for more hospital-based joint-clinic management of cardiodiabetes, the Group considered that current healthcare policy and commissioning of services place the GP in a key position as a major point of patient care.

Balancing national drives with patient care can present dilemmas. Quality and Outcomes Framework (QOF) programmes encourage GPs to manage chronic diseases, such as diabetes, to specific set targets. QOF initiatives, although highly laudable, work to surrogate end points and pre-set targets do not always deliver the optimal treatment goal for a given patient. Taking too rigid an approach to patient care can mean that aspects of a patient's total risk profile and clinical needs are overlooked. Studies such as the United Kingdom Prospective Diabetes Study (UKPDS) and the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) provide the evidence and support the view that treatment strategies to reduce diabetes and cardiovascular disease should be based on assessment of all risk factors, rather than based only on numerical thresholds for individual risk factors.[5,6,7]

The evidence for aggressive management of the multiple risk factors associated with CVD and diabetes is summarised in the form of existing practice guidelines such as those of the JBS 2[8] and ESC-EASD.[1] GPs should be encouraged by the clinical evidence and by guidelines to aim for higher rates of patient control for glycaemia, blood pressure and lipid targets. Local specialist champions in diabetes and cardiovascular disease can play an educational and skill-support role in helping GPs to work to targets appropriate to a patient's overall risk profile.

There may be scope for creation of multidisciplinary teams with a focus on cardiodiabetes, particularly for the referral of cases that require specialist appraisal, treatment or care services.

Collaborative care: the barriers

Issues over infrastructure can affect the optimal management of one-stop clinics at hospital and primary care level. Time, efficiency and resource limitations are affected as much by politics and policy as by clinical factors or a disease label. In addition, some specialists have professional resistance to being drawn into primary care and away from hospital-based practice.

On the positive side, one-stop clinics in the community, where a specialist physician together with a team of nurses provide protocol-based evaluations and management, can streamline the process of patient review and can work well if the attending specialist and the primary care team have opportunities to communicate and share case experiences. On the negative side, such clinics run the risk of offering too rigid an approach to patient assessments and may fail to tap into the wider range of clinical expertise and services that can be offered at specialist centres.

The Group agreed that communication is key to breaking down barriers that prevent collaborative approaches to patient care.

The clinical evidence – cardiovascular risk factors in patients with diabetes

Clinical evidence that patients with diabetes have multiple risk factors for cardiovascular disease is undeniable (a full review of the evidence is outside the scope of this report). Current practice guidelines from the Joint British Societies identify the risk faced by patients with diabetes and provide a framework for managing those risks in order to improve patient outlook.[8]

Patients are increasingly interested in understanding their disease. The Group recommended that they should be encouraged to know the nature and the levels of their modifiable risk factors and the targets set for reducing these risks.

More still needs to be done to promote public health messages based on known cardiovascular risk factors. Campaigns to encourage healthy lifestyles and to discourage obesity are the responsibility of government but can be supported by physicians and their professional societies. At a more localised level, a combined approach to managing diabetes and cardiovascular disease risk factors offers a way forward in reducing cardiovascular events and deaths.

'GPs are key to the delivery of cardiodiabetes patient care and more support should be given to those with a special interest in diabetes and cardiovascular disease'

Conclusions

Cardiodiabetes acknowledges the inter-relationship between diabetes and cardiovascular disease and the term creates a meaningful label for both physicians and patients. It also denotes a need to consider risk factors beyond glycaemic control and weight management. Collaborative care must be offered to cardiodiabetes patients, founded on clinical evidence and drawing on both specialist expertise and primary care skills. Communication and experience exchange are key elements for its success ●

Discussion

Q: ***Would the Group advocate an 'umbrella' speciality to deal with cardiodiabetes?***

A: We debated this at length. While there is some justification for taking a single-stop approach to patient care, we believe that specialist knowledge still has a key place in ensuring that patients are referred for particular expert investigations and consultations. We think that common approaches across the specialities, taking heed of guidelines such as those provided by NICE and JBS 2, are the way to ensure optimal patient care.

Q: ***There is no doubt that different specialities are already influenced by an awareness of the need to think beyond their own disciplines when managing patients with diabetes. How do you see the role of GPs?***

A: Today's GP has a key role in the day-to-day management of the patient and in helping with disease prevention. We consider a good GP with a well-trained team to be essential. The Primary Care Cardiovascular Society is going from strength to strength and good GPs can help to keep patients out of hospital. What we need to facilitate are means of ensuring that the hospital and specialists do not become the last resort but that they add value to community-based care and can identify and deal with complex cases.

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New versus old cardiometabolic markers of risk

Chair

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Introduction

New biomarkers, with the potential to serve as indicators of cardiovascular risk, are continually emerging. The validity of several of these was examined by this round table Group, who assessed the merits of biomarkers as additions or replacements to those markers currently in clinical use.

Estimated glomerular filtration rate (eGFR)

Reporting of eGFR started in April 2006, having been advocated in Part 2 of the National Service Framework for Renal Services.[1] Testing for this biomarker has a dual function. It helps to identify patients with impaired chronic renal dysfunction at an early stage and, more importantly, it is proving to be a strong marker of adverse cardiovascular (CV) outcomes. Several databases, e.g. the Kaiser Permanente patient registry, show a clear gradient of increased CV risk in parallel with deteriorating renal function as measured by eGFR.[2] The Reykjavik study[3] suggests there is an eGFR threshold of 60 ml/min/1.73 m^2, below which the risk of CV events increases independently of other risk factors. A very low eGFR suggests the risk of CV death may be increased by as much as 40%, independent of other CV risk factors, such as advanced age, dyslipidaemia and raised blood pressure.[3]

Age correction is important when interpreting whether a result is normal. Renal function is stable up until age 40, but thereafter 0.7 to 0.9 ml/min is lost per year in the normal (healthy) population. By age 80, the prevalence of an eGFR of 60 ml/min/1.73 m^2 or less may be greater than 70%.[4] Nevertheless, a low eGFR is still associated with increased CV risk, probably indicating subclinical atherosclerosis.

The group acknowledged that testing eGFR is a procedure for outpatient or primary care settings, whereas in acute settings creatinine is a more useful indicator of impaired renal function.

Low eGFR: to treat or not to treat

There is confusion currently about whether to treat a low eGFR in the absence of other uncontrolled risk factors and whether traditional treatments, such as statins, used in cardiovascular prevention can reverse renal impairment. Nephrologists advise that patients with a low eGFR should not be referred to a renal specialist unless proteinuria is present but angiotensin-converting enzyme (ACE) inhibitors can be started before this point.

'Brain-type natriuretic peptide (BNP) is primarily a marker of cardiac mortality'

A declining eGFR in younger patients (<70 years) can indicate that a more aggressive approach to CV risk factor management is needed. There is little evidence to support this, but most clinical trials of statins have excluded patients with signs of renal dysfunction. A retrospective meta-analysis of more than 19,000 patients with impaired renal function, who received either pravastatin or placebo, did suggest a benefit from a statin. The analysis included outcomes among patients who had normal kidney function at entry but could be categorised into high, medium or low normal values. Receiving a statin had a beneficial impact on outcomes among those with high normal creatinine values, with approximately 6% absolute risk reduction for CV events.[5]

Risk factor interventions are less likely to be helpful in patients with advanced kidney disease or among those receiving dialysis, the Group maintained, since their pathology involves arterial calcification and stiffness rather than lipid-related problems. It is not known whether lipid-lowering therapy has any impact on renal function and risk reduction in this group, and in any case diabetic patients with advanced renal disease are likely to be already undergoing aggressive treatment with risk-factor modifying medications.

The Group concluded that plentiful data support use of eGFR as a marker for identifying individuals at

high risk of CVD and that it could add value to risk scoring systems. The absence of clinical trial data means the Group were uncertain of the value of including a population-screening tool that has no evidence base for changing management. GPs, they felt, would be better advised to screen patients for proteinuria and to aim to lower blood pressure to a target of 125/75 mmHg when this is found. Routine screening for microalbuminuria is currently not advocated.

High-density lipoprotein (HDL) cholesterol

Low levels of HDL cholesterol (below 1.0 mmol/L) are well recognised to be a cardiovascular disease risk factor and the Group debated whether there should be wider screening for this. Levels are not routinely measured currently (except in diabetes) as there have been few well-tolerated interventions. Full lipid analyses of low-density lipoprotein (LDL) cholesterol, HDL cholesterol and triglycerides should be carried out in patients with diabetes, however, as low HDL-C levels are common in this group.

Specific HDL cholesterol treatment targets are not recommended in National Institute for Health and Clinical Excellence (NICE) or Joint British Societies' (JBS 2) guidelines[6,7] although a European consensus panel advocated a minimum target of 1.03 mmol/L in patients with coronary heart disease (CHD) or a high level of CHD risk.[8]

Most statins will raise HDL cholesterol slightly (approximately 0.05 – 0.1 mmol/L) but the Group believed that this only had a small impact on outcomes. Lifestyle interventions, such as smoking cessation, exercise and weight loss, will improve HDL cholesterol by around 5 to 10%, while fibrates and nicotinic acid will raise levels by 5 to 15%, and 15 to 30%, respectively.[9]

'Routine measurement of high-sensitivity C-reactive protein (hs-CRP) is inadvisable, except in acute care settings'

The NICE lipid modification clinical guideline states that nicotinic acid should not be offered for the primary prevention of CVD. It may be considered for secondary prevention in people with CVD who are not able to tolerate statins.[6] The NICE type 2 diabetes clinical guideline gives no general recommendation on the use of nicotinic acid in people with type 2 diabetes due to limited outcome trials in patients of this type.[10]

The Group recommended that patients with low HDL cholesterol levels should be managed to increase these to a target of 1.0 mmol/L since epidemiological data have shown an increased risk of CV mortality for levels below this.[8] An early trial of nicotinic acid demonstrated that intervention reduced CV events, but some Group members felt that hard prospective clinical trial outcome data were needed.

Raising HDL cholesterol is more difficult in elderly patients due to the side effects of current drugs. An alternative strategy is to lower LDL cholesterol aggressively to provide greater gains in absolute risk reduction, although there were concerns about this approach due to a lack of data for women and older people in primary prevention.

Lifestyle intervention, including weight reduction, smoking cessation and increasing exercise, should be recommended for individuals with low levels of HDL cholesterol.

Table 1. Factors raising high-sensitivity C-reactive protein

- Inflammatory processes, such as atherosclerosis
- Adiposity
- Smoking
- Intercurrent illnesses
- Hormone replacement therapy in post-menopausal women
- Diabetes or metabolic syndrome

High-sensitivity C-reactive protein (hs-CRP)

The biomarker hs-CRP is not available for measurement routinely in most clinical laboratories but it is gaining credibility in the research community from epidemiological studies as an emerging marker of increased

Table 2. Merits of other biomarkers of cardiovascular risk

Apolipoproteins

- Difficult and expensive as only a few specialist centres measure these counts
- Debatable whether counts add value to treatment decisions
- Non-HDL-C atherogenic particle counts can be estimated by subtracting HDL cholesterol from total cholesterol.
- Prospective Studies Collaboration in Oxford[18] suggests best predictor of CV risk is total cholesterol: HDL cholesterol ratio but no comparative data yet to show whether patients identified in this way do any better on specific treatments than patients identified by LDL-cholesterol levels
- Levels of atherogenic non-HDL cholesterol identify patients with high residual risk who might benefit from higher doses of statins or a statin with the addition of ezetimibe
- It is unclear whether apolipoprotein profiles differ and correlate with CVD in patients with type 2 diabetes or in South Asian patients.

BNP

- Brain-type natriuretic peptide (BNP) is released from the left ventricle in response to increased wall tension
- Studied as a predictive and prognostic marker of heart failure and of occult coronary artery disease in symptomatic and asymptomatic patients[19]
- Patients with the highest NT-proBNP quartile levels (above 460 pg/ml) are more likely to have clinical risk factors for adverse cardiovascular events[20]

Troponin

- Biomarker of choice for detecting cardiac injury
- Provides additional information to BNP – if both raised, patients are at very high risk; if both low, patients are considered low risk after acute coronary syndromes.[21]

CV risk.[11] Hs-CRP values show a gradient of relative risk,[12] with increased risk linked to CHD death and non-fatal myocardial infarction (MI).

Many factors can raise hs-CRP values (**table 1**). Hs-CRP values are also raised when LDL cholesterol or triglycerides are high and when HDL is low, but offer independent risk prediction to these variables.[13]

Statins consistently lower hs-CRP and some analyses suggest that this 'on-treatment' hs-CRP lowering predicts benefit, but an outcomes benefit is difficult to show due to the many causes of raised hs-CRP. Furthermore current hs-CRP-lowering treatments have other effects and any causal role of hs-CRP will need to be established by outcome trials of specific hs-CRP inhibitors.

'It is debatable whether apolipoproteins can aid clinical decision-making'

The Group were uncertain whether hs-CRP plays a causal role in increasing CV risk or is merely a marker of other pathological processes in progress. No European or British recommendations give advice on hs-CRP but a consensus statement of the American Heart Association and Centers for Disease Control and Prevention recommends considering using hs-CRP to screen patients with intermediate CV risk (10–20% by Framingham calculation over 10 years) on a population basis using a cutpoint of hs-CRP >3 mg/L to identify high-risk groups.[14] Hs-CRP is more closely associated with stroke than LDL cholesterol so, theoretically, lowering hs-CRP with statins or by other means would benefit patients at increased risk of stroke.[15]

Measuring hs-CRP routinely, other than in acute care settings, was considered currently inadvisable by the Group. Factoring hs-CRP into computer risk algorithms could potentially enable up to 50% of intermediate-risk patients to be reclassified correctly as being in a higher or lower risk category group.[16] Better classification and appropriate intervention adjustment has tremendous potential for generating cost savings. High-sensitivity CRP measurement would only be useful for patients not identified as being at increased CV risk by other means.

The Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial was designed to assess the effectiveness of a statin in the primary prevention of cardiovascular events in individuals with normal LDL-C and elevated hs-CRP.[17] The results of this are awaited. Many interventions lower hs-CRP, including lifestyle changes, such as exercise and Mediterranean diet, blood pressure reduction, establishing good glycaemic control and glitazones.

The Group was divided as to whether they would consider using a more powerful statin or adding ezetimibe to a statin to treat the lipids of patients with high hs-CRP readings more aggressively. Outcome data are needed to justify the strategy.

Other biomarkers of CV risk

Other biomarkers of CV risk include apolipoproteins, brain-type natriuretic peptide (BNP) and troponin. Their merits relative to other biomarkers of risk, such as LDL and HDL cholesterol, are summarised in table 2[18–21]

Discussion

Q: ***What about the use of isoprostane?***

A: This is a promising early biomarker of CV risk from oxidative stress and endothelial dysfunction, although assays are probably not robust.

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Managing cardiovascular risk in 'at-risk' populations

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Introduction

Cardiovascular risk assessment is currently very topical, with much debate about measurement and targets. Recent guidelines from the National Institute for Health and Clinical Excellence (NICE) on modification of blood lipids have provided helpful advice.[1]

The Group began by performing a SWOB analysis to examine the **S**trengths, **W**eaknesses, **O**pportunities and **B**arriers that exist in managing cardiovascular risk in at-risk populations.

Early detection of relevant risk factors was clearly a very important ***strength*** because disease in one territory may signify possible disease elsewhere. The proposed National Screening Project will go some way to address this issue. Early management is also important because treatment has been shown to be cost-effective.[2]

The NICE lipid modification clinical guideline and the Joint British Societies' Guidelines (JBS 2) recommend that a strategy should be put in place to identify everyone over the age of 40 who is likely to be at high cardiovascular (CV) risk.[1,3] The Group agreed that it would be a strength for people to know their overall risk, rather than simply the levels of individual risk factors.

A major **weakness** in the management of cardiovascular risk is that many people carry a portfolio of risk factors. Using data from the Health Survey for England (2003), it has been estimated that at 20% cardiovascular disease (CVD) risk or higher, about 23% of men and 8% of women aged 40–74 years are potentially eligible for treatment (recognising that the Framingham equation has limitations).[3]

Since the evidence base in the elderly is not strong, there is uncertainty about how aggressively to treat older patients. The Group discussed the difference between the chronological age and the biological age of the patient, and concluded that judgements in this area rested with the skill of the physician. Some prescribed medications have unacceptable side effects, which makes management more difficult. Communication between the specialities, and between primary and secondary care, is critical to management of the at-risk individual.

The ***opportunities*** afforded by management of CV risk include engagement of patients, reduced events, improvement of quality of life and improved prognosis.

The ***barriers*** to management of CV risk are cost; the need for a clear follow-up policy and better communication between primary and secondary care; the need for education in this disease area; a gap in expectation between what physicians think patients were doing and what they are actually doing; lack of exercise; increasing obesity; and the consumption of unhealthy food, smoking and alcohol that is so prevalent in our society.

Identification of at-risk patients

The Group agreed with the JBS 2 recommendation that people with established cardiovascular disease and those who were asymptomatic but had an estimated multifactorial CVD risk >20% over 10 years should have equal priority for CVD prevention.[3] The 'hazardous waist' was thought to be a useful indicator of the metabolic syndrome and risk factors that need to be addressed; and Group members were keen to risk-stratify hypertensives and to look for those with end-organ damage.

By contrast, the NICE lipid modification clinical guideline[1] clearly distinguishes between primary and secondary prevention. It specifies that primary prevention patients with ≥20% 10-year CVD risk should 'discuss the need for risk reduction with their doctor and if a statin is appropriate, simvastatin 40 mg (or a drug of similar efficacy and acquisition

'Better communication between healthcare professionals is helpful in managing risk'

cost) should be initiated. If there are potential drug interactions or if simvastatin 40 mg is contraindicated, a lower dose of simvastatin or pravastatin may be offered. Higher intensity statins should not be routinely offered to people for the primary prevention of CVD. There is no target level for total or low-density lipoprotein (LDL) cholesterol for people who are treated with a statin for primary prevention of CVD.'

The Group talked about calculating risk, including the Framingham[4] and QRISK[5] models. The Scottish ASSIGN risk calculator is appropriate for the population of Scotland.[6] Deprivation and lifestyle were agreed to be important, as was the role of family history. One patient in 500 has a family history of familial hypercholesterolaemia, with more than 80% going undetected.[7] Family history of cardiomyopathy and sudden death should also be included. Erectile dysfunction is a marker of endothelial dysfunction for patients who may be at future vascular risk.[8]

It was agreed that risk stratification could be refined further using additional criteria such as 24-hour blood pressure and full lipid profile.

Risk modification

A key question concerning the Group was when risk factors should be treated to target and when to use a 'fire and forget' approach, in which the patient receives a pre-determined treatment without any requirement to follow up relevant parameters. After some debate, there was a consensus that it was important to treat the high-risk patient to target and that 'fire and forget' would be reasonable for those at low risk. This contrasts with the NICE lipid modification clinical guideline,[1] which does not recommend a target level for total or LDL cholesterol for primary prevention of CVD.

In terms of modification of risk, the Quality and Outcomes Framework (QOF)[9] has moved things forward. In 2007, for example, 81.9% of patients with coronary heart disease achieved the QOF target of 5.0 mmol/L for total cholesterol.[10]

The Group felt that, for the high-risk under-75s, physicians should be aiming for the JBS 2 targets of 4.0 and 2.0 mmol/L[3] but targets of 5.0 and 3.0 mmol/L might be more appropriate for a population approach to primary prevention, unless it became possible to risk-stratify patients more accurately. Patients over 75 years are more difficult to manage than those under 75 years but they are also the population at the highest risk. Over-75s with a long expected lifespan should be targeted for intensive therapy but more research is necessary to define which patients should receive this treatment.

Follow-up

The discussion then turned to follow-up and who should be responsible for continued follow-up. Good discharge information is particularly important, as the information needs to be incorporated into GP databases. Summaries generated by computer database may generate more helpful discharge documents than handwritten summaries.[11]

A one-stop hospital review would be valuable to ensure that all the loose ends were tied up, but thereafter follow-up would be most cost-effective in the community. Vascular clinics, for example, could be set up in primary care for patients with known CVD, diabetes and coronary heart disease.

Much of the work in these clinics could be done by nurses and healthcare assistants. They would be useful in encouraging patients to 'know their numbers'. The NICE lipid modification clinical guideline[1] states that "once a person has been started on a statin for primary prevention, repeat lipid measurement is unnecessary. Clinical judgement and patient preference should guide the review of drug therapy."

Barriers and solutions

The key barriers remained: cost, poor follow-up, poor communication between primary and secondary care, poor education, the ageing population and lack of evidence in older patients, poor concordance with medications given to patients, and the unhealthy food lobby.

The health service needed a multidisciplinary approach in which all the disciplines would give patients the same messages and goals. This would require better communication between primary and secondary care – the Group felt it was a pity that face to face meetings between GPs and consultants had diminished in the last few years as they represented a lost opportunity to communicate, develop team working and share experiences

Discussion

Q: *What are the top three solutions?*

A: First, the population should know their numbers and their CVD risk, which would give them ownership of their own health. More education was still needed on how to use treatments effectively, how to target patients and what goals to aim for. Lastly, better communication between primary and secondary care would ensure patients received the right treatment in the right place at the right time.

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USES

As adjunctive therapy to diet in:

Primary hypercholesterolaemia: For co-administration with an HMG-CoA reductase inhibitor (statin) for patients with primary (heterozygous familial and non-familial) hypercholesterolaemia not appropriately controlled with a statin alone. *Monotherapy:* For use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated. *Homozygous Familial Hypercholesterolaemia (HoFH):* For co-administration with a statin, for use in patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis). *Homozygous sitosterolaemia (phytosterolaemia):* For use in patients with homozygous familial sitosterolaemia.

Studies to demonstrate the efficacy of 'Ezetrol' in the prevention of complications of atherosclerosis have not yet been completed.

DOSAGE AND ADMINISTRATION

For oral administration

Put patients on an appropriate lipid-lowering diet and continue during treatment.

Recommended dose is one 'Ezetrol' 10 mg tablet daily, administered at any time of the day, with or without food.

When added to a statin, either continue with the indicated usual initial dose of that particular statin or the already established higher statin dose. Consult the statin dosage instructions.

Co-administration with bile acid sequestrants: Dosing should occur either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant.

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Use in paediatric patients: Children <10 years: Not recommended as no clinical data are available.

Use in hepatic impairment

No dosage adjustment is required with mild hepatic insufficiency (Child Pugh score 5 to 6). Not recommended in patients with moderate (Child Pugh score 7 to 9) or severe (Child Pugh score >9) liver dysfunction.

CONTRA-INDICATIONS

Hypersensitivity to any component. When co-administered with a statin, refer to the statin SPC. 'Ezetrol' co-administered with a statin during pregnancy and lactation. 'Ezetrol' co-administered with a statin in patients with active liver disease or unexplained persistent elevations in serum transaminases.

PRECAUTIONS

Liver enzymes: When co-administered with a statin, perform liver function tests at initiation of therapy and according to the statin SPC. *Skeletal muscle:* In post-marketing experience with 'Ezetrol', myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with 'Ezetrol'. However, rhabdomyolysis has been reported very rarely with 'Ezetrol' monotherapy and very rarely with the addition of 'Ezetrol' to other agents known to be associated with increased risk of rhabdomyolysis. If myopathy is suspected based on muscle symptoms or is confirmed by a creatinine phosphokinase (CPK) level >10 times the ULN, immediately discontinue 'Ezetrol', any statin, and any of these other agents. Advise all patients starting therapy with 'Ezetrol' of the risk of myopathy and to report promptly any unexplained muscle pain, tenderness or weakness *Hepatic insufficiency:* Not recommended in patients with moderate or severe hepatic insufficiency due to the unknown effects of the increased exposure to 'Ezetrol'. *Fibrates* The safety and efficacy of co-administration have not been established. There is a possible risk of cholelithiasis and gall-bladder disease in patients receiving fenofibrate and 'Ezetrol'. If suspected, conduct gall-bladder investigations and discontinue co-administration. *Ciclosporin:* Exercise caution when initiating 'Ezetrol' in patients taking ciclosporin and monitor ciclosporin concentrations. *Warfarin, another coumarin anticoagulant or fluindione:* Monitor the International Normalised Ratio (INR) if taken together with 'Ezetrol'. *Excipient:* 'Ezetrol' tablets contain lactose: do not use in patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

Interactions (studies have only been performed in adults): Colestyramine: Concomitant colestyramine administration decreased the mean AUC of total 'Ezetrol' approximately 55%. The incremental low-density lipoprotein cholesterol (LDL-C) reduction due to adding 'Ezetrol' to colestyramine may be lessened by this interaction. *Statins:* No clinically significant pharmacokinetic interactions were seen upon co-administration with atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, or rosuvastatin. Ezetrol API.EZE.08.UK.2903 Page 3 September 2008 All printed versions of this SOP are Uncontrolled Copy and are for information only. This document was printed on 10 September 2008 and is valid for this date only

Pregnancy and lactation: 'Ezetrol' co-administered with a statin is contra-indicated during pregnancy and lactation, refer to the SPC for that particular statin.

Pregnancy: 'Ezetrol' should be given to pregnant women only if clearly necessary. No clinical data are available on the use of 'Ezetrol' during pregnancy.

Lactation: 'Ezetrol' is contra-indicated.

Driving and using machines: Dizziness has been reported.

SIDE EFFECTS

Refer to SPC for complete information on side effects

Clinical studies

In clinical studies where 'Ezetrol' was administered alone or with a statin, adverse reactions were usually mild and transient. The overall incidence of side effects reported with 'Ezetrol' was similar between 'Ezetrol' and placebo. Similarly, the discontinuation rate due to adverse experiences was comparable between 'Ezetrol' and placebo.

The following common (≥1/100, <1/10) drug-related adverse experiences were reported in patients taking 'Ezetrol' alone (n=1,691) or co-administered with a statin (n=1,675), or with fenofibrate (n=185):

'Ezetrol' administered alone:

Nervous system disorders: headache. *Gastro-intestinal disorders:* abdominal pain and diarrhoea.

'Ezetrol' co-administered with a statin:

Nervous system disorders: headache and fatigue. *Gastro-intestinal disorders:* abdominal pain, constipation, diarrhoea, flatulence and nausea. *Musculoskeletal and connective tissue disorders:* myalgia.

'Ezetrol' co-administered with fenofibrate:

Gastro-intestinal disorders: abdominal pain.

Laboratory values

In controlled clinical monotherapy trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥3 X ULN, consecutive) was similar between 'Ezetrol' (0.5%) and placebo (0.3%). In co-administration trials, the incidence was 1.3% for patients treated with 'Ezetrol' co-administered with a statin and 0.4% for patients treated with a statin alone. These elevations were generally asymptomatic, not associated with cholestasis, returning to baseline after discontinuation of therapy or with continued treatment.

In clinical trials, CPK >10 X ULN was reported for 4 of 1,674 (0.2%) patients administered 'Ezetrol' alone vs 1 of 786 (0.1%) patients administered placebo, and for 1 of 917 (0.1%) patients co-administered 'Ezetrol' and a statin vs 4 of 929 (0.4%) patients administered a statin alone. There was no excess of myopathy or rhabdomyolysis associated with 'Ezetrol' compared with the relevant control arm (placebo or statin alone). Ezetrol API.EZE.08.UK.2903 Page 4 September 2008 All printed versions of this SOP are Uncontrolled Copy and are for information only. This document was printed on 10 September 2008 and is valid for this date only

Post-marketing experience

The following additional adverse reactions have been reported in post marketing experience. Because these adverse experiences have been identified from spontaneous reports, their true frequencies are not known and cannot be estimated.

Blood and lymphatic system disorders: thrombocytopenia. *Immune system disorders*: hypersensitivity including rash, urticaria, anaphylaxis and angioedema. *Psychiatric disorders*: depression. *Nervous system disorders*: dizziness, paraesthesia. *Gastro-intestinal disorders:* nausea, pancreatitis. *Hepatobiliary disorders:* hepatitis, cholelithiasis, cholecystitis. *Musculoskeletal and connective tissue disorders:* arthralgia, myalgia, myopathy/rhabdomyolysis. *Laboratory values:* increased transaminases, increased CPK.

PACKAGE QUANTITIES AND BASIC NHS COST

28 Tablets: £26.31

Marketing Authorisation number

PL 19945/0001

Marketing Authorisation holder

MSD-SP Limited

Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK

POM **Date of review of prescribing information: September 2008**

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