# Macrovascular disease in diabetes

## Henrietta Mulnier

This, the sixth article in the series "Fundamentals in Diabetes", addresses macrovascular disease in diabetes. The author quantifies the risk of macrovascular disease in diabetes and puts this risk into perspective. She explores the use of risk calculators and the treatment guidelines currently in place, as well as the difference between treatment goals and targets and the priorities that must be considered in the future. Finally, ways of helping people to achieve treatment targets through effective self-management are discussed.

Macrovascular disease is the primary cause of death in diabetes and is two to four times more likely to occur in individuals with diabetes than in those without (Kannel et al, 1979; Morrish et al, 2001; Mulnier et al, 2006; Soedamah-Muthu et al, 2006; Mulnier et al, 2008; Vamos et al, 2012). In the UK, £9 billion per year is spent on treating diabetes, of which a sizeable portion is spent on trying to prevent cardiovascular disease (CVD) and its associated mortality (Luengo-Fernández et al, 2006; Diabetes UK, 2010). Considering macrovascular disease as the primary cause of death in diabetes, the recently published 2007–2008 UK mortality data highlight the devastating impact of diabetes, as the crude mortality rate per 1000 per year at risk is 35.53 in people with diabetes versus 0.86 in people without diabetes (NHS Information Centre for Health and Social Care, 2011). These data also show that, although in diabetes death rates are higher in men than women (30% higher in type 1 and 21% higher in type 2), the relative risk (RR) associated with diabetes is greater in women than in men, so the cardiovascular benefits of being female appear to be lost in diabetes. The RR is also greater in younger adults and decreases with age. In comparison to age-equivalent peers without diabetes, the mortality risk in young women is nine times greater in those with type 1 diabetes and six times greater in those with type 2 diabetes, but in men the RR is four times greater in both those with type 1 and type 2 (NHS Information Centre for Health and Social Care, 2011). The 2007–2008 RR profiles for women and young adults are very similar to those seen in macrovascular disease from the 1990s reported in UK data, and the excess risk in women also reported previously (Kanaya et al, 2002; Huxley et al, 2006; Soedamah-Muthu et al, 2006; Mulnier et al, 2008). Although there is some evidence from hospital episode data to suggest that the incidence rates of myocardial infarction (MI) and cerebrovascular accidents (CVAs) are lowering in people with diabetes, unlike those without diabetes, mortality rates for people admitted with angina are still increasing (Vamos et al, 2012). Therefore, current trends in statistics suggest that mortality from macrovascular disease in diabetes may not have changed in the last decade, despite advances in clinical care, guidance from NICE and SIGN and the Quality and Outcomes Framework (QOF). This problem of poor outcome in diabetes is not

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unique to the UK and has been reported in the US and Norway, again highlighting the need to treat individuals with diabetes more effectively (Dale et al, 2008; Ford, 2011).

Data regarding the effects of smoking on people with diabetes also help to emphasise the alarming impact that this long-term condition has on CVD risk. Smoking in a person with diabetes has a distinct effect on renal function, causing rapidly accelerated deterioration in renal function and resultant renal failure in smokers who have diabetes (Chuahirun and Wesson, 2002; Hovind et al, 2003). Thus, people with diabetes should be encouraged to stop smoking. However, the large and significant increase in macrovascular risk and mortality associated with being a smoker that is seen in the general population is not apparent in people living with type 2 diabetes (Doll et al, 2004). There is a much smaller difference in mortality and macrovascular disease risk between being a smoker or non-smoker than is observed in those without diabetes. There is also no statistical difference in risk between being a smoker and an ex-smoker, whereas in the general population there is a large and significant difference (Tuomilehto et al, 1996; Mulnier et al, 2006). This is certainly not a statistic to be promoted, but it shows the extreme vascular insult and effect that type 2 diabetes has on the endothelial lining, so much so that smoking has no additional impact on the risk of having an MI or a CVA in type 2 diabetes (Tuomilehto et al, 1996; Mulnier et al, 2006).

## Pathophysiology and causative mechanisms

In the first paper of this series, the pathophysiological effects of diabetes on the endothelial wall were described (Lockman et al, 2011). In essence, hyperglycaemia leads to oxidative stress and an associated cytokine cascade resulting in accelerated atherosclerosis (Orasanu and Plutzky, 2009). The same process occurs in type 1 and type 2 diabetes, but the metabolic syndrome may explain why a 55-year-old woman with type 2 diabetes is at the same increased RR as a woman of the same age with type 1 diabetes, even though the apparent diabetes duration is very different (Mulnier et al, 2008). Although microvascular disease may be detected earlier and is an indicator of macrovascular disease, it is the resultant MI and CVA associated with macrovascular disease that increase mortality risk (Morrish et al, 2001; Abdelhafiz et al, 2011). It is as yet unclear which risk factor – hyperglycaemia, hypertension, dyslipidaemia, inactivity or something we are yet to measure – is the biggest contributor to developing macrovascular disease.

## Risk calculation and screening

Cardiovascular risk estimation in diabetes is complex. The current risk calculators, which have been created on the basis of a large set of epidemiological data from the general population, have been shown to be inaccurate in diabetes (Yeo and Yeo, 2001; Coleman et al, 2007). This is likely to be owing to people with diabetes being at an increased risk of macrovascular disease compared with people without diabetes (Juutilainen et al, 2005; Mulnier et al, 2008; Vamos et al, 2012). NICE guidance currently recommends that people with diabetes should be informed that risk calculators give an estimate only (NICE, 2009). However, when an individual has several risk factors contributing to a CVD risk estimate of over 20% in 10 years, then the likelihood of an error from those calculators is reduced (NICE, 2009). If a person with diabetes is considered not to be at high CVD risk (*Box 1*), then the UKPDS (UK Prospective Diabetes Study) risk engine can be used to calculate that person's risk annually (Diabetes Trials Unit, 2012). Although the potentially de-motivating impact of a high-risk estimate should be assessed before discussing this with a person at risk, perhaps the greatest benefit will be gained from using the software to show a reduction in risk after lifestyle and treatment changes have been effective.

As microvascular disease is a predictor of macrovascular disease, screening for retinopathy and nephropathy is essential (Rosenson et al, 2011). Retinal images should be graded annually by a trained practitioner in a quality-controlled service (NICE, 2009). At diagnosis – and this is of particular importance in type 2 diabetes – the

> **Box 1. NICE considerations for cardiovascular risk assessment (NICE, 2009).**
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> According to NICE guidance, a person is considered 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 anti-hypertensive therapy).
> - Does not have microalbuminuria.
> - Does not smoke.
> - Does not have a high-risk lipid profile.
> - Has no history of cardiovascular disease **and** no family history of cardiovascular disease.

retina should be assessed to detect damage due to any prolonged period of undiagnosed hyperglycaemia. If retinal damage has already occurred, it is essential not to improve glycaemic control too quickly as this may worsen existing damage (Diabetes Control and Complications Trial Study Group, 1998). As a general rule, whenever attempts are made to improve poor glycaemic control, it is prudent to wait for retinal screening results before dramatic improvement is made. An initial dose can be used to reduce excessive hyperglycaemia and then titrated appropriately after retinal screening results become available. If, or once, a large drop or change in control has occurred, it is also advisable to re-screen the retina.

Annual testing of the albumin:creatinine ratio (ACR) in an early morning urine sample is recommended to detect the early stages of renal disease. If the ACR is raised (>2.5 mg/mmol for men, >3.5 mg/mmol for women) in three samples within 3–4 months, then treatment with an angiotensin-converting-enzyme (ACE) inhibitor should be started and the patient monitored (NICE, 2009). Local guidance will dictate at which point people should be referred to a specialist renal service, usually when or before the estimated glomerular filtration rate (eGFR) falls to below 30 mL/min.

## Targets and treatment to reduce risk

### Clotting, cholesterol and blood pressure
Until recently, aspirin had been given routinely in the primary prevention of ischaemic heart disease in diabetes. However, recent research has suggested that routinely prescribing aspirin for primary prevention may not be appropriate in people at risk of haemorrhage (Belch et al, 2008; Ogawa et al, 2008). This is another complex area of risk management in diabetes that requires careful clinical assessment and judgement in each case.

The NICE guidance recommends that anyone with a blood pressure of <145/90 mmHg should be offered 75 mg of aspirin daily, although the SIGN guidance suggests that aspirin should not be used routinely for primary prevention (SIGN, 2010). The latest American Diabetes Association (ADA) guidance recommends that anyone with a 10-year CVD risk of >10% should take 75 mg of aspirin daily, but those at low risk (10-year risk <5%) should not be offered aspirin, and clinical judgement should be used for those with a 5–10% 10-year risk (American Diabetes Association, 2012). The risks and benefits should be discussed with each patient and a collaborative decision made in each case.

Treating dyslipidaemia or raised total cholesterol (or both) with statins in people with diabetes reduces the risk of MI by 36% and CVA by 48% (Colhoun et al, 2004). Although there is an associated risk of myopathy (0.1%) and rhabdomyolysis (0.15 per 1 000 000 prescriptions), the benefits of statin treatment clearly outweigh the risks (Ballantyne et al, 2003). For individuals aged 40 years and over, statin therapy should be commenced unless they are not at risk from CVD (*Box 1*; NICE, 2009). A fibrate may be appropriate if triglycerides are raised (NICE, 2009). A total cholesterol of <4 mmol/L and triglycerides at 2.3–4.5 mmol/L should be the treatment target, but age and potential pregnancy must also be considered.

Maintaining blood pressure at <140/80 mmHg (<130/80 mmHg if microvascular disease is present) has a similar risk benefit as that of effective cholesterol management (UKPDS, 1998a; NICE, 2009). Cholesterol and blood-pressure management are simple and achievable in comparison with glycaemic control, and the onus should be on the health service to encourage concordance with medication. People with diabetes should be helped to appreciate the benefits of treatments and encouraged to use self-management skills and tools, such as dosing boxes. Combination therapy may also help to improve compliance in some polyphamacy.

Weight loss has a direct impact on insulin resistance, so lifestyle changes should always be recommended. Bariatric surgery has proved successful, in some cases even reversing diabetes, and should be considered in those with a BMI >35 kg/m² (Mingrone et al, 2012). A recent study has shown CVD risk to be reduced and diabetes to be reversed even in those with a BMI starting as low as 30–35 kg/m² (Cohen et al, 2012).

## Glycaemic control

The target for glycaemic control is far less clear. The UKPDS showed that for every 1% reduction in $HbA_{1c}$ there was an 11% drop in cardiovascular mortality risk and suggested that an $HbA_{1c}$ levels at <42 mmol/mol (6%) may be optimal (UKPDS, 1998b; Stratton et al, 2000). A subsequent report from the UKPDS described a significant macrovascular risk reduction in intensively treated patients after a 20-year follow-up (Holman et al, 2008). A study of multi-factorial treatment in people with newly diagnosed type 2 diabetes has shown a non-significant reduction in cardiovascular events, whereas an earlier study has demonstrated that multi-faceted treatment of type 2 diabetes significantly reduced cardiovascular complications, including a 53% risk reduction in macrovascular disease in those with established diabetes under the age of 70 years old (Gaede et al, 2008; Griffin et al, 2011). Other more recent studies have contradicted earlier evidence, with one study by the group ACCORD (Action to Control Cardiovascular Risk in Diabetes) demonstrating that those in an intensively treated arm had an increased risk of death when treated to a target $HbA_{1c}$ of <42 mmol/mol (6%) (ACCORD Study Group et al, 2008; Duckworth et al, 2009). Interestingly, the increased risk of mortality remained for the final 3 years of follow-up, despite relaxation of the glycaemic control and consequent removal of the risk of severe hypoglycaemia, suggesting the contribution of something other than tight glycaemic control to be the cause of this maintained excess mortality rate (ACCORD Study Group et al, 2011).

These studies have caused much debate over what level of $HbA_{1c}$ should be recommended and the evidence is still far from clear. The lack of clear guidance may well be leaving young people at an unnecessarily high risk from hyperglycaemia, while older people may still

be too tightly controlled with an HbA$_{1c}$ target of 58 mmol/mol (7.5%). Risk plotted against rising HbA$_{1c}$ produces a "U-shaped curve", although the relationship becomes linear when the population is sub-divided by 10 year age-bands over 60 years of age (Huang et al, 2011). This suggests that individuals aged over 60 years should not be treated to an HbA$_{1c}$ level of <48 mmol/mol (6.5%), but it is still unclear as to what the target HbA$_{1c}$ should be for people aged <60 years. With the hugely increased RRs observed in those aged <60 years, perhaps the evidence from the Diabetes Control and Complications Trial and the UKPDS should still be adhered to, with people being treated to a target as close to normal as possible (Diabetes Control and Complications Trial Research Group, 1993; Stratton et al, 2000).

## Treatment

In regard to treatment options, the NICE and SIGN guidelines are clear and evidence-based, although concordance, risk of hypos, and cost impact on choice (NICE, 2009; SIGN, 2010). Metformin treatment is simple initially, but more complicated when the eGFR declines. Lactic acidosis associated with metformin is relatively rare and evidence for its incidence is poorly reported, whereas the library of evidence for hyperglycaemia causing death and the benefit from treatment with metformin is vast (van Berlo-van de Laar et al, 2011). Individuals with a reduced eGFR, who are known to benefit from metformin treatment, are likely to experience escalating poor control when it is withdrawn too soon, but what is too soon and what is safe? The evidence is unclear and local guidance is usually based on anecdotal evidence. This is an area in urgent need of proper investigation.

Sulphonylureas are recommended by NICE as second-line treatment, although hypoglycaemia can be a problem. However, the occurrence of hypoglycaemia in these agents suggests that they are effective and that the problem lies with patient education, self-management skills or a combination of the two. Any person treated with sulphonylureas should be given guidance around hypos and those at high risk of hypos should avoid sulphonylureas. The dipeptidyl peptidase-4 (DPP-4) inhibitors are weight-neutral and associated with a very low risk of hypoglycaemia, and thus can be a good option in older-age groups at risk from severe hypoglycaemic episodes. One of the DPP-4 inhibitors is safe to use in individuals with a reduced eGFR and even in renal failure, because clearance is via the liver. Together with low-dose metformin, this may be an extremely effective treatment option for an older person.

Glucagon-like peptide-1 (GLP-1) agonists continue to raise interest. Clinically, the benefits of weight loss and improved glycaemic control are huge in some people with diabetes, while in others there can be little or no benefit. At present, GLP-1 treatment is limited to people with poor glycaemic control and a BMI >35 kg/m$^2$ according to NICE, and >30 kg/m$^2$ according to SIGN. However, GLP-1 is licensed as a glucose-lowering agent. Weight loss was an incidental finding in the randomised controlled trials and is now referred to as a side effect. The general guidance that people must be over a certain BMI to start GLP-1 and, in particular, the NICE recommendation that they must lose weight as well as improve their HbA$_{1c}$ to stay on the treatment, is perhaps limiting a very good agent to an inappropriately small select group of patients, as well as asking too much of them. What we really need to know is which people are most likely to respond to the glucose-lowering effects of GLP-1. Perhaps it would be more sensible to limit it to people with proven beta cell function, but until we have an economical and easily performed measure of beta cell function it is difficult to offer advice other than that, and for some people, a 3-month trial of GLP-1 may prove worthwhile.

## Self-management

It is very clear that a person who lives with diabetes has many decisions to make. They need to balance risks and benefits and find the self-motivation to change behaviour. Focus and adequate funding to support patient education and promote empowerment and self-management skills is needed. Patient-centred care planning using realistic goal setting, together with

guidance on medical management, is a big step in the right direction. DSNs should be encouraged to ensure consultations are patient-centred. When care planning and structured education are included in the QOF targets, people with diabetes who are not diet-controlled and who, like most, do not find diabetes "easy" to manage will finally have the support that they need to control their diabetes and reduce their risks of macrovascular disease and an early death.

## Conclusion

The mortality rates, absolute risk and relative risk of macrovascular disease in diabetes remaining so high gives cause for concern. It is essential that all DSNs are able to help people with diabetes reduce their risk of macrovascular disease effectively, as current practice is clearly not sufficient despite the many health initiatives of recent years. DSNs really need to assess how they "help" people with diabetes to self-care and achieve targets. In addition, commissioners need to consider focusing on funding effective management and education strategies in an effort to improve outcomes in people with diabetes. If structured education and self-management are considered effective, then it is these initiatives that need to be funded. Unfortunately, it is very difficult to prove whether a person reporting positive feedback from a course and a slight concomitant drop in $HbA_{1c}$, weight and blood pressure, will actually have reduced their 10-year risk of diabetes, but evidence suggests that the approach to date has not been effective and that we do need to work differently. ∎

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