A Review of Risk Factors and Cardiovascular Disease in Diabetes Care - 2011

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This review presents results from recent trials and observational studies on risk factors and cardiovascular disease. Treatment goals are provided that should be preferable for most patients in diabetes care, even if these recommendations should be combined with clinical judgement and individual preferences.

HbA1c as risk factor for cardiovascular disease

Evidence exists today from observational studies that hyperglycemia is an important risk factor for cardiovascular diseases, with a risk increase per 1%-unit increase in HbA1c of 27% in type 1 diabetes (1) and 11-16% in type 2 diabetes (2, 3), independently of clinical characteristics and other traditional risk factors. A risk reduction by glucose-lowering has most obviously been demonstrated in patients with type 1 diabetes, often younger or middle-aged with less traditional risk factors than patients with type 2 diabetes.

The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study of 1,182 patients with type 1 diabetes found a relative cardiovascular disease (CVD) risk reduction of 40%, adjusted for other risk factors including albuminuria, when comparing two groups of mean HbA1c 7.4% and 9.1% followed-up observationally for 11 years (4). These results were recently strongly underlined in the larger observational Swedish National Diabetes Register (NDR) study of 7,545 patients with a relative risk reduction of 37% for coronary heart disease (CHD) and 41% for CVD, comparing two groups of mean HbA1c 7.2% and 9.1% followed for 5 years (5).

The glucose lowering effect on CVD risk in type 2 diabetes has been a matter of debate in recent years, according to results in three trials, Action to Control Cardiovascular Risk in Diabetes (ACCORD) (6), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) (7) and Veterans Affairs Diabetes Trial (VADT) (8), showing non-significant differences in CVD risk between intensified and standard treatment (with a HbA1c difference of around 1%) in patients with mean diabetes duration 8-11 years and one-third with a history of CVD.

The older United Kingdom Prospective Diabetes Study (UKPDS) in newly detected patients found a borderline significant relative risk reduction for myocardial infarction (MI) of 16% (p=0.052) when comparing groups with mean HbA1c 7.0% and 7.9% followed for ten years (9), although a 39% lower MI risk in a subgroup of overweight patients treated with metformin (10), and a post-trial 10-year observational study in all UKPDS patients could demonstrate a significant MI risk reduction of 15% (11).

Even if ACCORD found an increased risk of total and CVD mortality after 3 years, post-hoc analyses have shown that a decrease in CVD mortality occurred in intensively treated patients who indeed reached the HbA1c target 6% (12). Furthermore, meta-analyses of these trials have been able to demonstrate significant relative risk reductions of 15% for MI and 11-15% for CVD, as well as no significant risk increase with regard to total or CVD mortality (13-16). These summarised findings in the meta-analyses were underlined in a recent 5-year observational NDR study of 18,334 patients with type 2 diabetes. It showed relative risk reductions of 20% for CHD and 16% for CVD (p<0.001) when comparing two groups of mean HbA1c 6.5% and 7.5%, adjusted for clinical characteristics and traditional risk factors, a similar HbA1c difference of 1% as in the trials (2). Furthermore, subgroup of patients with longer diabetes duration (mean 14 years) or of patients with a history of CVD showed adjusted 6-year CVD event rates increasing with higher baseline or updated mean HbA1c with no J-shaped curves at lower HbA1c levels (2).
A recent observational UK General Practice Research Database (GPRD) study has reported increased risk of total mortality with lower HbA1c with lowest risk for HbA1c 7.5%, and also a 49% higher risk of total mortality with insulin treatment versus oral agents (17). However, this was not verified in the NDR study, showing no J-shaped risk curve for total mortality in patients treated with insulin or oral agents, and that the increased risk of total mortality with insulin was due almost exclusively to an increased risk of non-CVD mortality, and that HbA1c was not at all associated with non-CVD mortality (2).

**HbA1c in a national survey**

The Swedish NDR is a national register since 1996 performing as a tool for local quality assurance in diabetes care, with annual reports during patient visits at hospitals and primary health care centres nationwide by trained physicians and nurses. The register nowadays covers more than 70% of all Swedish patients with type 2 diabetes and far higher percentage of patients with type 1 diabetes. Cross-sectional surveys in the NDR in 2008 showed that mean HbA1c was 7.1±1.3% in 21,000 patients with type 1 diabetes, and 6.2±1.2% in 171,000 patients with type 2 diabetes (18). Those with type 1 diabetes who achieved the HbA1c target <8% were 49% in 2008, and this proportion had increased considerably since previous surveys from 43% in 1999 onwards. Those with type 2 diabetes who achieved the HbA1c target <7% were 52% in 2008, and this proportion had increased considerably since previous surveys from 37% in 1999 onwards.

**Glycemic goals**

A reasonable goal for many non-pregnant adults should be <7%. A lower target can be applied for selected individuals, if achieved without significant hypoglycemia, including patients with short diabetes duration and long life expectancy.

A higher target may be appropriate in patients with a history of severe hypoglycemia, short life expectancy, extensive comorbid conditions, or longstanding diabetes with difficulty to achieve the general goal despite treatment efforts.

According to results in the observational NDR study (2), the general goal of <7% can be applied in patients with a history of CVD (37% of all patients with type 2 diabetes in the NDR) and in patients with longer diabetes duration (47% of all patients with type 2 diabetes in the NDR had duration 7 years or more), even if further studies should be of value in such patients.

**Blood pressure as a risk factor for CVD**

UKPDS has demonstrated a linear relationship between mean in-study systolic blood pressure (SBP) and the risk of macro- and microvascular complications (19). The recent randomised ACCORD-blood pressure (BP) trial has shown no difference in CVD risk with systolic blood pressure (SBP) <120 and <140 mmHg (20), while the risk for the pre-specified secondary endpoint, stroke, was reduced with intensive therapy, HR 0.59 (0.39-0.89;P=0.01). The trial ADVANCE-BP showed reduction in combined CVD and microvascular events with SBP <135 versus 140 mmHg (21).

The observational International Verapamil-Trandolapril Study (INVEST) found no difference in risk of total mortality or nonfatal CVD between SBP <130 and 130-139 mmHg, but increased risk of total mortality with SBP <110 versus 125-129 mmHg (22). The observational NDR-BP found no difference in CVD risk between SBP 110-129 and 130-139 mmHg, but increased risk with baseline SBP 110-129 mmHg and further SBP reduction from baseline to follow-up (23). Both INVEST and NDR-BP found increased CVD risk with SBP >140 mmHg, HR 1.44-1.46 (P<0.001).

**Blood pressure in a national survey**

A cross-sectional survey in the NDR of 21,000 patients with type 1 diabetes in 2008 showed mean BP 126/73 mmHg, and 71% achieved SBP <130 mmHg (18). Cross-sectional surveys of patients with type 2 diabetes in the NDR showed a decrease in mean BP from 141/77 mmHg in 2005 to 136/76 mmHg in 2009, and uncontrolled BP >140/90 mmHg decreased from 58% to 46% (24).

**Blood pressure goals**

Recent randomised clinical trials and observational studies support a SBP goal well below 140 mmHg, and below 135 mmHg based on data from ADVANCE (21).

With regard to the risk for stroke, the BP goal could be even lower, although taking into account the increased risk of total mortality seen with very tight SBP control <110 mmHg. The diastolic BP goal should be <80 mmHg.

**Hyperlipidemia as risk factor for CVD**

Evidence exists from observational studies that LDL-cholesterol is an strong risk factor for cardiovascular diseases, with a risk increase of 17% per 1 mmol/l increase (25) or 5-17% per 1 SD increase in LDL-cholesterol (25, 26) in type 2 diabetes, independently of clinical characteristics and other traditional risk factors. Concerning HDL-cholesterol, a risk decrease of 29% per 1 mmol/l increase (25) or 16-17% per 1 SD increase (25, 26) has been shown in type 2 diabetes. ATP III has also identified non-HDL cholesterol (representing the sum of atherogenic LDL and VLDL lipoproteins) as a secondary treatment target, in patients with increased triacylglycerol (TG) or HDL cholesterol values (27).

Randomised controlled trials have established the clinical benefits of lowering LDL-cholesterol levels for risk reduction of coronary heart disease (CHD) (28). However, the observational fenofibrate intervention and event lowering in diabetes (FIELD) and NDR studies could demonstrate that the ratio non-HDL-to-HDL-cholesterol had a stronger effect on CHD risk than LDL-cholesterol, with relative CHD risk increases of 21-28% per 1 SD increase in non-HDL/HDL in patients with type 2 diabetes (22, 26). Furthermore, the NDR study could demonstrate that when patients within the lowest tertile of a lipid measure were compared to those with all lipid measures in highest tertile, adjusted HR for CHD was 0.62 with non-HDL/HDL <3.5, but a higher HR 0.70 with LDL <2.5 mmol/L. The lowest tertile of LDL corresponds to the treatment targets according to US and European guidelines (27, 29-31). At the same time, the curve of the 5-year CHD rate showed a steep and linear decrease by lower levels of non-HDL/HDL, verifying the concept “the lower the better for blood lipids”, while the curve by LDL only was slowly and slightly decreasing at lower levels below 3 mmol/L.
Finally, mean TG:HDL was considerably lower in patients within lowest tertile of non-HDL:HDL, 0.82±0.47, than in those within lowest tertile of LDL <2.5 mmol/l, 1.49±1.03 (25). TG:HLR1 representing diabetic dyslipidaemia, should be regarded as a marker for insulin resistance primarily involving the glycosyn synthesis pathway (32). Accumulating evidence to date indicate that insulin resistance significantly contributes to accelerated atherosclerosis and development of cardiovascular diseases (32-36).

**Blood lipids in a national survey**

A cross-sectional survey in the NDR of patients with type 1 diabetes in 2004 showed mean LDL-cholesterol 2.7±0.8 mmol/l, HDL-cholesterol 1.6±0.5 mmol/l and TG 1.1±0.6 mmol/l (37). Those of all 17-21,000 patients who achieved the target LDL <2.5 mmol/l were 48% in 2004 and 2008 (18). Comparatively, patients with type 2 diabetes treated with lipid lowering drugs in 2007 showed mean LDL-cholesterol 2.5±0.8 mmol/l, HDL-cholesterol 1.3±0.3 mmol/l, TG 1.7±0.8 mmol/l (38). Those of all 172,000 patients in 2008 who achieved LDL-cholesterol <2.5 mmol/l were 45%, those achieving HDL-cholesterol >1.0 mmol/l in men and >1.2 mmol/l in women were 61%, and those with TG <1.7 mmol/l were 56% (18).

**Goals for blood lipids**

The primary goal for LDL-cholesterol should be <2.5 mmol/l in patients without a history of CVD, while a lower goal of <1.8 mmol/l is an option in individuals with overt CVD.

ATP III has also identified non-HDL cholesterol <3.3 mmol/l as a secondary treatment target, in patients with TG >2.3 mmol/l and/or HDL cholesterol <1.0 mmol/l (47).

With regard to the NDR study comparing non-HDL:HDL and LDL-cholesterol (25), a target for non-HDL:HDL of <3.3 (based on non-HDL cholesterol <3.3 and HDL cholesterol >1.0 mmol/l) could be an option instead of the primary LDL target suggested in recent guidelines, also as the non-HDL:HDL target should achieve lower levels of TG:HDL.

**Overweight and obesity as risk factor for CVD**

Current evidence suggest that BMI is an independent risk factor for CVD, with a risk increase of 13% per 5 units increase of BMI, independently of clinical characteristics and traditional risk factors, as shown in a 6-year observational NDR study of patients with type 2 diabetes (39). The relative CVD risk increase was 24% (p<0.001) with overweight (BMI 25-29.9 kg/m²) compared to normal weight (18-24.9 kg/m²), and 44% (p<0.001) with obesity (>30 kg/m²) compared to normal weight, as also verified for CHD in the Nurse’s Health Study (40), and for stroke with BMI >35 versus 20-24 kg/m² in the UK GPRD study (41), although not shown in newly detected patients in the UKPDS (42, 43).

**BMI in a national survey**

Cross-sectional surveys with regard to life-style factors in patients with type 1 diabetes in the NDR 2005-08 have shown mean BMI 25.7±4.2 kg/m², obesity in only 14%, 36% were overweight, more than half were exercising >3 times per week, and 12% were smokers in middle age (18). On the contrary, patients with type 2 diabetes have shown a clear negative trend with increasing BMI to 29.5±5.2 kg/m² in 2008, with a high proportion 41% of obesity, elevated waist circumference, and as many as 22% smokers in middle age. However, almost half exercised 3 times or more per week.

**BMI goals**

The BMI goal for patients with type 1 and type 2 should be <25 kg/m². It remains to be seen if on-going trials like the Look Action for Health in Diabetes (AHEAD) study (44) will be able to demonstrate a significant risk reduction of CVD with intensified weight reduction. A pronounced weight reduction of 20% of initial weight following bariatric surgery has been shown to achieve a risk reduction in total mortality of 29% compared to stable weight when followed-up for ten years in the Swedish Obese Subjects (SOS) study (10% with diabetes) (45).

**Multi-factorial approach**

Additive effects of blood pressure and glucose have been demonstrated in the ADVANCE trial (46), and also reported in observational data from UKPDS (47), NDR (48), the Multiple Risk Factor Intervention Trial (49) and the Diabetes Intervention Study (50). The efficiency of a multi-factorial approach as the best way to reduce diabetic complications, with use of evidence-based pharmacological treatment in addition to efficient life-style measures, has convincingly been shown in the long-term follow-up of type 2 diabetic patients with microalbuminuria in the Steno-2 Study (51).

Estimates of the CVD risk based on multiple risk factor predictors can be used as prognostic information and support for the choice of therapeutic strategies. Physicians engaged in diabetes care should have an interest in the assessment of risk of developing any major CVD event using a general CVD risk assessment tool. A new risk model for 5-year CVD risk in type 1 diabetes has recently been presented, based on an observational study of 3661 patients, presenting risk evaluation with 8 predictors including HbA1c, systolic BP, ratio total-to-HDL-cholesterol, smoking and albuminuria, and with good performance when validated regarding calibration and discrimination (52).

Estimates of 5-year risk have been proposed as being more accurate than 10-year risk estimates (53), and have also been applied in some risk model designed for type 2 diabetes, the Hong Kong CHD risk score (54) and the New Zealand CVD risk score (55). The UKPDS risk model estimating 10-year risk of MI (56) or CVD (57) is most widely used and has been recommended for practice guidelines (58), although nowadays considered to have poor calibration in more recent samples of patients with type 2 diabetes (59-63). To enhance prediction of 5-year CVD risk in type 2 diabetes patients, a new risk model has recently been presented based on 12 predictors including HbA1c, systolic BP, ratio total-to-HDL-cholesterol, BMI, smoking and albuminuria, with adequate performance when validated regarding calibration and discrimination (64).
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