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COMMENTARY

Dysglycaemia, dyslipidaemia and hypertension: risk factors primarily focused on the disease or risk estimates primarily focused on the patient?

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A diagnosis of diabetes independently increases the future risk of serious cardiovascular outcomes by up to threefold in women and twofold in men [1]. This relationship has been demonstrated in scores of prospective studies [2–6] and in administrative databases. For example, in one database comprising all residents of the province of Ontario, Canada, the 6 year incidence of death in middle-aged and older men with a history of diabetes did not differ from that of middle-aged and older men with a recent myocardial infarction [7]. Reasons for this strong relationship remain unclear and many hypotheses continue to be considered. However, as diabetes is defined on the basis of an elevated glucose level, much attention has focused on glucose or glycation of various molecules. Indeed, many prospective studies have noted a strong relationship between elevated glucose or HbA_{1c} levels and incident cardiovascular outcomes that is independent of history of diabetes. Indeed, this relationship extends well below the glycaemic thresholds used to diagnose diabetes [8] and into the normal range for the general population [2, 9–11]. Thus, elevated fasting glucose, post-load glucose or HbA_{1c} levels (i.e. dysglycaemia) are related to cardiovascular outcomes [12] in a manner that is similar to the relationship between dyslipidaemia or elevated blood pressure and cardiovascular outcomes [13–15]. Whether this means that cardiovascular outcomes are caused by an elevated glucose level, insufficient metabolic action of insulin (which allows the glucose to rise) or other associated biological abnormalities cannot be discerned from these data and, indeed, remains unclear [16].

Knowing that a particular risk factor such as HbA_{1c}, lipid level or blood pressure is related to future cardiovascular outcomes clearly expands our understanding of cardiovascular disease and leads to future research hypotheses. A risk factor for a disease (or outcome) is therefore primarily focused on the disease, and the associated relative risk or relative hazard can be viewed as a ‘disease-centred’ metric. This metric provides little information on the risk of cardiovascular outcomes in a particular patient with this risk factor. Such information is best conveyed by the absolute risk or incidence of the outcome, which can be viewed as a ‘patient-centred’ metric. Moreover, patients typically have many risk factors for cardiovascular outcomes, which together confer a very different personal risk of disease than could be predicted on the basis of any one risk factor alone. Recognition of this fact has led to the development of various risk scores [17–19]. These patient-centred scores integrate age and other easily measured risk factors to generate a personalised estimate of absolute risk or incidence for an individual patient. These scores clearly only incorporate a fraction of the more than 100 statistically independent risk factors that have been identified for cardiovascular outcomes [20]. However, they show that for clinical care, knowledge of several risk factors provides more information about a particular patient’s chance of suffering a cardiovascular event than knowledge of the level of any one risk factor alone.

The difference between disease-centred risk factors and patient-centred risk estimates is beautifully illustrated in the most recent analysis of data from the EPIC-Norfolk prospective study by Chamnan et al. in this issue of *Diabetologia* [21]. The authors studied 10,144 people (of whom 44% were men and 4.8% had diabetes) with a mean

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age of 57 years who were free of cardiovascular disease. Participants had baseline measurements of HbA_{1c}, blood pressure, cholesterol, HDL-cholesterol and other risk factors, and were followed for a mean of 10 years with prospective ascertainment of cardiovascular outcomes. Consistent with many other studies, the authors clearly demonstrated that the risk of incident cardiovascular events progressively rose with age, smoking, age-adjusted HbA_{1c} levels ≥5.5%, systolic blood pressure levels ≥130 mmHg, total cholesterol:HDL ratios ≥4 and progressively lower HDL-cholesterol levels below 1.5 mmol/l. These data once again confirm that these are important risk factors for cardiovascular outcomes.

The authors then took this information to the (virtual) bedside to show how information about several risk factors is more relevant to an individual patient's risk than information on one isolated risk factor. They compared the clinical usefulness of information based on the HbA_{1c} alone (classified as either <5.5%, 5.5–5.9% or 6.0–6.4%) as a single risk factor with the usefulness of cumulative information based on age, sex, smoking, lipids and blood pressure. They found that people in the highest HbA_{1c} group who were females and non-smokers, and in the lowest category of age, lipids and blood pressure, had a lower incidence of cardiovascular outcomes than people in the lowest HbA_{1c} group who were male, smokers, and in the highest category of age, lipids and blood pressure. They also found that once these factors were taken into account, knowledge of the HbA_{1c} level provided little additional information on the incidence of cardiovascular outcomes. Exactly the same approach was then applied to: (1) the cholesterol:HDL ratio; and (2) systolic blood pressure. Thus people in the highest cholesterol:HDL group who were females, non-smokers, and in the lowest category of age, systolic blood pressure and HbA_{1c} had a lower incidence of cardiovascular outcomes than people in the lowest cholesterol:HDL group who were males, smokers, and in the highest category of age, systolic blood pressure and HbA_{1c}. Similarly, people in the highest systolic blood pressure group who were females, non-smokers, and in the lowest category of age, cholesterol:HDL and HbA_{1c} had a lower incidence of cardiovascular outcomes than people in the lowest systolic blood pressure group who were males, smokers, and in the highest category of age, cholesterol: HDL and HbA_{1c}.

These analyses show that the HbA_{1c} level behaves like other established risk factors for cardiovascular disease and that the best estimate of the future incidence of a cardiovascular outcome requires the integration of many risk factors and should not be based on the measurement of any one risk factor alone, be it dysglycaemia, dyslipidaemia, hypertension, inflammation, abdominal obesity or others.

What conclusions can be drawn from this and other papers on this topic? First, there is a clear difference between identification and characterisation of a risk factor, and using one or more risk factors to estimate the incidence or absolute risk of a disease. The information provided by risk factors (and relative risks or hazards) is focused on the disease and can thus best inform further research and insights into pathophysiology. Risk estimates (and absolute risks or risk scores), on the other hand, provide information that is focused on the patient and can therefore best inform clinical management of that patient. Second, patients do not present with one abnormality and should not be characterised or treated on the basis of any one abnormality. Rather, the totality of available information, based on setting, history, physical examination and clinical investigations, should be integrated to generate an estimate of individual risk. This estimate can then help to identify the most appropriate management. Third, dysglycaemia, dyslipidaemia and hypertension all behave similarly as risk factors for cardiovascular outcomes and provide much more information on the incidence of cardiovascular outcomes when they are combined than when considered separately. Indeed, it is very likely that most other identified independent cardiovascular risk factors would behave in a similar way. Fourth, assessment of a patient's risk of suffering an outcome based on knowledge of several risk factors can certainly identify people with the greatest need for risk-reduction therapies, but provides little information regarding the best interventions to mitigate that risk. These interventions can only be reliably identified from randomised clinical trials of thousands of participants, which generally require several years of follow-up. For cardiovascular outcomes in people with diabetes, such trials have already demonstrated the efficacy of blood pressure lowering [22], ACE inhibitors [23], statins [24, 25] and bypass surgery [26], but have generated mixed results on glucose lowering [27, 28].

In summary, (1) detecting risk factors for disease, (2) using several risk factors to estimate a particular patient's risk, (3) identifying the menu of appropriate therapies from those proven in reliable clinical trials, and then (4) integrating this information into the patient's overall clinical presentation to determine optimal management will clearly optimise the clinician's ability to truly provide the best evidence-based care.

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References

1. Huxley R, Barzi F, Woodward M (2006) Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ 332:73–78
2. Sarwar N, Gao P, Seshasai SR et al (2010) Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 375:2215–2222
3. Selvin E, Marinopoulos S, Berkenblit G et al (2004) Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med 141:421–431
4. Selvin E, Coresh J, Golden SH, Brancati FL, Folsom AR, Steffes MW (2005) Glycemic control and coronary heart disease risk in persons with and without diabetes: the atherosclerosis risk in communities study. Arch Intern Med 165:1910–1916
5. Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N (2004) Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. Ann Intern Med 141:413–420
6. Gerstein HC, Pogue J, Mann JF et al (2005) The relationship between dysglycaemia and cardiovascular and renal risk in diabetic and non-diabetic participants in the HOPE study: a prospective epidemiological analysis. Diabetologia 48:1749–1755
7. Booth GL, Kapral MK, Fung K, Tu JV (2006) Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. Lancet 368:29–36
8. American Diabetes Association (2010) Diagnosis and classification of diabetes mellitus. Diab Care 33(Suppl 1):S62–S69
9. Gerstein HC, Islam S, Anand S et al (2010) Dysglycaemia and the risk of acute myocardial infarction in multiple ethnic groups: an analysis of 15,780 patients from the INTERHEART study. Diabetologia. doi:10.1007/s00125-010-1871-0
10. Held C, Gerstein HC, Yusuf S et al (2007) Glucose levels predict hospitalization for congestive heart failure in patients at high cardiovascular risk. Circulation 115:1371–1375
11. Gerstein HC, Swedberg K, Carlsson J et al (2008) The hemoglobin A1c level as a progressive risk factor for cardiovascular death, hospitalization for heart failure, or death in patients with chronic heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program. Arch Intern Med 168:1699–1704
12. Gerstein HC (2010) More insights on the dysglycaemia–cardiovascular connection. Lancet 375:2195–2196
13. Neaton JD, Wentworth D, Research Group MRFIT (1992) Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316,099 white men. Arch Int Med 152:56–64
14. Lewington S, Whitlock G, Clarke R et al (2007) Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet 370:1829–1839
15. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R (2002) Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 360:1903–1913
16. Punthakee Z, Werstuck GH, Gerstein HC (2007) Diabetes and cardiovascular disease: explaining the relationship. Rev Cardiovasc Med 8:145–153
17. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB (1998) Prediction of coronary heart disease using risk factor categories. Circulation 97:1837–1847
18. Conroy RM, Pyorala K, Fitzgerald AP et al (2003) Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 24:987–1003
19. Almeda-Valdes P, Cuevas-Ramos D, Mehta R, Gomez-Perez FJ, Aguilar-Salinas CA (2010) UKPDS Risk Engine, decode and diabetes PHD models for the estimation of cardiovascular risk in patients with diabetes. Curr Diabetes Rev 6:1–8
20. Brotman DJ, Walker E, Lauer MS, O'Brien RG (2005) In search of fewer independent risk factors. Arch Intern Med 165:138–145
21. Chamnan P, Simmons RK, Jackson R, Khaw KT, Wareham NJ, Griffin SJ (2010) Non-diabetic hyperglycaemia and cardiovascular risk: moving beyond categorisation to individual interpretation of absdolute risk. Diabetologia. doi:10.1007/s00125-010-1914-6
22. Patel A, Macmahon S, Chalmers J et al (2007) Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 370:829–840
23. Heart Outcome Prevention Evaluation (HOPE) Study Investigators (2000) Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO HOPE substudy. Lancet 255:253–259
24. Colhoun HM, Betteridge DJ, Durrington PN et al (2004) Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 364:685–696
25. Collins R, Armitage J, Parish S, Sleigh P, Peto R (2003) MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5,963 people with diabetes: a randomised placebo-controlled trial. Lancet 361:2005–2016
26. Frye RL, August P, Brooks MM et al (2009) A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med 360:2503–2515
27. Turnbull FM, Abraira C, Anderson RJ et al (2009) Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia 52:2288–2298
28. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA (2008) 10-Year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 359:1577–1589