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COMMENTARY

Commentary on the United Kingdom Prospective Diabetes Study outcomes model 2: Need for long-term follow up and quality of life data in Asian patients

A paper by Hayes *et al.*[1] published in *Diabetologia* in June 2013 reports an updated version of the United Kingdom Prospective Diabetes Study (UKPDS) outcomes model developed on the basis of data from 5,102 patients from the original UKPDS and 4,031 survivors enrolled in the 10-year post-trial study. Given the longevity of patients with diabetes, there is no doubt that accurate simulation of lifetime outcomes requires data with a minimum follow-up period of more than 10 years.

Considerable efforts have been devoted to developing models for simulating outcomes of patients with diabetes. Such models can be useful in two different situations: first, medical decision-making; for example, recommendation of statin therapy based on absolute cardiovascular risk; and second, health technology assessment based on efficacy and cost-effectiveness. In the UK, the standard of care recommended by the health technology assessment body – the National Institute for Health and Clinical Excellence (NICE) – are determined on the basis of the results of clinical trials and cost-effectiveness analysis. Sitagliptin is, for example, recommended by NICE Short Clinical Guideline 87 as an additional agent instead of a sulfonylurea in second-line therapy because of its incremental cost-effectiveness ratio of £1,567 per one quality-adjusted life year (QALY) as compared with rosiglitazone[2].

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In that analysis, the QALY of diabetes patients was estimated by computer simulation using the UKPDS outcomes model.

Table 1 summarizes previously developed health economic models for diabetes. A health economic model for diabetes generally consists of three elements: disease states and transitions; risk equations; and utility values of each disease state ranging from 0 to 1. The incidence of a diabetic complication is viewed as a transition from a 'no-complication' state to the disease state. The probabilities of each transition depend on the risk factors shown in Table 1, and the relationships between the probabilities and the risk factors are expressed as risk equations[1,3–6]. Simulation by the UKPDS outcomes model 2 is carried out as the following steps on an annual cycle. First, at time-point $t = 0$, risk factors and event history of patients are input into risk equations, yielding the probabilities of transition. Second, mortality is calculated at $t = 0$ by using a risk equation. Mortality depends on the first step; that is, it will be higher if a transition to a diabetic complication occurs at $t = 0$. Third, in the case of death, the calculation is terminated; otherwise, information on risk factors and event history is updated at $t = 1$, and the same calculation is repeated annually until death. A utility value, which is usually estimated by quality-of-life (QOL) questionnaires, reflects the quality of a patient's lifetime with the corresponding diabetic complication. The simulated lifetime is weighted by utility values to account for its quality, yielding an estimate of QALY. For more details, see supplementary materials in Hayes *et al.*[1]

Among the models in Table 1, the UKPDS outcomes model 2, the JJ risk engine[3] and the risk equations from the Swedish National Diabetes Register[4] were developed by using individual patient data, but the others were constructed by synthesizing summary statistics reported in the literature, such as incidence rate and mean QOL value[5,6]. The UKPDS followed more than 4,000 patients for the longest period, making it possible to simulate end-stage events, such as second myocardial infarction and stroke. Furthermore, QOL data are available only in the UKPDS[1]. Although their follow-up length was relatively long, the Japanese study observed few incidents of second cardiovascular events, blindness, end-stage renal disease or amputation as a result of their low incidence and the limited sample size[3]. In contrast, the Swedish National Diabetes Register is a registry of data from clinical practice, so although it has a large sample size, the incidence of diabetic complications has not been adjudicated by a central committee as is usually done in prospective studies[4].

As expected, cardiovascular risks vary across study populations: the incidence of myocardial infraction and stroke per 1,000 person-years were, respectively, 11.3 and 5.6 in the UK[1], and 13.5 and 12.1 in Sweden[4]. By contrast, those of coronary heart disease and stroke were 7.6 and 7.1, respectively, in the Japanese study[3]. Given the apparent lower risk of coronary heart disease in Japan, models developed in Caucasian populations should not be used

Table 1 | Summary of health economic models for diabetes

Study country	Data	Risk factors incorporated in risk equations	Disease states				QOL
			Cardiovascular	Eye	Renal	Other	
UKPDS[1] The UK	*n* = 5,102 30-year follow-up	Age, sex, duration of diabetes, ethnicity, smoker, SBP, HbA1c, LDL, HDL, BMI, eGFR, heart rate, atrial fibrillation, PVD, albuminuria, hemoglobin, white blood cells	MI, stroke, IHD, CHF	Blindness	Renal failure	Diabetic ulcer, amputation	Available
JDCS/J-EDIT[3] Japan	*N* = 1,748 8-year follow-up	Age, sex, duration of diabetes, current smoker, leisure-time physical activity, SBP, HbA1c, non-HDL cholesterol, BMI, albumin-to-creatinine ratio, atrial fibrillation	CHD, stroke	Progression of retinopathy	Overt nephropathy		No
SNDR[4] Sweden	*N* = 29,034 5-year follow-up	Age, sex, duration of diabetes, smoker, blood pressure, HbA1c, total-to-HDL cholesterol ratio, LDL, BMI, albuminuria, history of events before diagnosis	MI, heart failure, IHD, stroke				No
CDC[5] The USA	Literature-based	Age, sex, race or ethnicity, hypertension, hypercholesterolemia, current smoker	CHD, angina, cardiac arrest/myocardial infarction, stroke	Photocoagulation, blindness	Low- or high-macroalbuminuria, clinical nephropathy, ESRD	Peripheral nephropathy, lower extremity amputation	Available
CORE[6] Switzerland	Literature-based	Age, sex, duration of diabetes, race, smoker, blood pressure, HbA1c, lipid levels, BMI, baseline complications	MI, angina, CHF, stroke	Retinopathy, macular edema, cataract	Nephropathy	Neuropathy, PVD, foot amputation, hypoglycemia, ketoacidosis, lactic acidosis	Available

BMI, body mass index; CDC, Centers for Disease Control and Prevention; CHD, coronary heart disease; CHF, congestive heart failure; CORE, Center for Outcomes Research; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein cholesterol; IHD, ischemic heart disease; J-EDIT, Japanese Elderly Diabetes Intervention Trial; JDCS, Japan Diabetes Complications Study; LDL, low-density lipoprotein cholesterol; MI, myocardial infarction; PVD, peripheral vascular disease; QOL, quality of life; SBP, systolic blood pressure; SNDR, Swedish National Diabetes Register; UKPDS, United Kingdom Prospective Diabetes Study.

for simulation of Asian patients. To illustrate this, consider a Japanese man aged 60 years without diabetic retinopathy and atrial fibrillation who does not have smoking or exercise habits. The clinical characteristics of the patient are glycated hemoglobin 9%, duration of diabetes 20 years, body mass index 23 kg/m^2, systolic blood pressure 180 mmHg, total cholesterol 210 mg/dL, high-density lipoprotein cholesterol 60 mg/dL and albumin-to-creatinine ratio 60 mg/g. His 5-year risk of coronary heart disease calculated by the JJ risk engine is 9.3%, whereas that calculated by the UKPDS risk engine is 15.5%, giving an approximately 1.7-fold overestimation.

Health technology assessment is an emerging political issue in Japan – as indicated by the interim report published by Japan's Central Social Insurance Medical Council (Chuikyo) on 6 November 2013, cost-effectiveness using QALY as a default outcome measure is expected to be introduced in Japan to determine health insurance coverage or the price of pharmaceuticals and medical devices. As aforementioned, extrapolating models for diabetes to a population of different ethnicity is risky. Thus, there is an urgent need for long-term follow up and QOL data among Asian patients.

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