Risk Assessment Models for Diabetes Complications: A Survey of Available Online Tools

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Abstract. Predictions, risk assessment and risk profiling are among the various decision support techniques that medical professionals increasingly rely on to provide early diagnose in patients with elevated risks and to slow down the rapid increase in prevalence of chronic diseases. The introduction of risk assessment tools and applications for chronic diseases in large scale longitudinal clinical studies, presents many challenges due to the nature of the data (studies last around a decade) and the complexity of the models. In this paper, we give an overview of research work on risk assessment tools and applications for diabetes complications. We also introduce the REACTION project and its vision in the field of risk assessment for diabetes complications.

1 Introduction

Risk factors for diabetes complications have been intensively studied during the last decades, and these studies greatly improved the current scientific knowledge about the biological processes underlying diabetes. Risk factors have been commonly used in risk assessment models for the prediction of diabetes complications. Risk assessment models are the backbone of risk assessment tools used in the clinical practice. These tools as parts of clinical/medical applications are able to stratify diabetes patients according to their probability of developing complications or experiencing adverse events.

A risk assessment tool is based on one or more models which could be any type of algorithm or mathematical formula (e.g., a set of rules, a decision tree or a weighted sum) for assessing the overall statistical probability of certain situations to occur in the future. Medical risk assessment may provide probabilistic statements as the likelihood that certain complications may occur given the present and historic health status.

Several risk assessment models for diabetes complications have been proposed in the literature. In the overall clinical management of people with diabetes special attention has to be dedicated to the prevention of short-term as well as long-term complications. Even though “short” and “long term” are commonly used terms in the context of diabetes complications, there is not a clear and universally accepted

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distinction between the two; here thereafter, we indicate as short term complication any pathological process or event related to diabetes that is expected to arise within weeks or few months, while long term complications may arise even after several years. In the context of the REACTION project (see Section 5), our research group work exclusively on long term risk assessment models; thus, we consider short term models (especially insulin management tools) out of the scope of this paper.

The most common predictive risk assessment models for diabetes complications are not able to deal with all the major complications, but are mainly focused on cardiovascular diseases, coronary heart disease and diabetic retinopathy (long-term complications).

The paper is organized as follows: the major clinical studies for diabetes and its complications have been reviewed in Section 2, while in Section 3 the risk assessment tools and applications for diabetes complications have been examined. Advantages and limits of present tools are discussed in Section 4, while Section 5 presents the EU funded project REACTION, an ICT based initiative that will develop and integrate new risk assessment models for diabetes complications.

2 Major Clinical Studies for Diabetes

Long term risk assessment tools and applications are usually built upon data collected during large scale, longitudinal clinical studies. Such type of studies typically last around a decade, involve thousands of patients in numerous health centres, and measure different aspects of patient's clinical/medical profile. Thus, it is not surprising that the data collected in each study can be employed for deriving multiple risk assessment models, differing from each other for predicted outcomes, involved parameters or analytical techniques.

Some of the well known clinical studies related to diabetes complications which will be discussed here, are DCCT/EDIC [1], Qrisk [2] and UKPDS [3].

2.1 DCCT/EDIC Study

A study of long term risk assessment related to diabetes and complications is the Diabetes Control and Complications Trial (DCCT). DCCT [1] is a landmark medical study conducted by the United States National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The DCCT involved 1,441 volunteers, ages 13 to 39, with type 1 diabetes and 29 medical centres in the United States and Canada. DCCT is a multicenter, randomized clinical trial designed to compare intensive with conventional diabetes therapy with regard to their effects on the development and progression of the early vascular and neurologic complications. Volunteers had to have had diabetes for at least 1 year but no longer than 15 years. The study compared the effects of standard control of blood glucose versus intensive control on the complications of diabetes. Intensive control meant keeping glycated haemoglobin (HbA1c) levels as close as possible to the normal value of 6 percent or less.

A new study started after the DCCT, called Epidemiology of Diabetes Interventions and Complications (EDIC). EDIC [4] is a follow up study on 90% of the participants from DCCT that looked into cardiovascular disease and the effects of intensive control on quality of life and cost effectiveness.

2.2 Qrisk Study

Another large study in the field is the QRisk [2]. Qrisk aims to develop a cardiovascular disease risk algorithm which will provide accurate estimates of cardiovascular risk in patients from different ethnic groups in England and Wales and to compare its performance with the modified version of Framingham score recommended by the National Institute for Health and Clinical Excellence (NICE). QRisk study is based on a cohort of 2.3 million patients aged 35-74 with 140,000 cardiovascular events with and without diabetes. Overall population (derivation and validation cohorts) comprised 2.22 million people who were white or whose ethnic group was not recorded, 22,013 south Asian, 11,595 black African, 10,402 black Caribbean, and 19,792 from Chinese, other Asian or other ethnic groups.

Although Qrisk is not a study focused on diabetes (the initial cohort consisted of 0.61 million patients who were free of diabetes and existing cardiovascular disease) the consequently developed risk assessment Qrisk2 calculator takes as risk factor the presence of diabetes.

2.3 UKPDS Study

The United Kingdom Prospective Diabetes Study [3] (UKPDS) is a landmark randomized controlled trial which showed that both intensive treatment of blood glucose and of blood pressure in diabetes can lower the risk of diabetes-related complications in individuals newly diagnosed with Type 2 diabetes. The UKPDS cohort consists of 5,102 patients, followed for a median of 10.7 years. Between 1977 and 1991, general practitioners in the catchment areas of 23 participating UKPDS hospitals were asked to refer all patients aged 25 to 65 years presenting with newly diagnosed diabetes. Patients in the UKPDS had biochemical measurements, including HbA1c, blood pressures, and lipid and lipoprotein fractions, recorded at entry to the study, at randomization in the study after a three-month period of dietary therapy, and each year subsequently.

3 Risk Assessment Applications for Diabetes Complications

To our knowledge, almost all of the risk assessment applications for diabetes complications provide risk profiles in real time. Most of these tools compute complications related to cardiovascular diseases, but it is also possible to find calculators for kidney failure, eye problems and foot problems. For short term diabetes complications there is no tool or software available. The risk assessment applications for diabetes complications resulting from this research and discussed in this section are: Diabetes PHD, Qrisk2, Framingham, Risk Score calculator, UKPDS Risk Engine and HARP.

3.1 Diabetes PHD

Diabetes PHD [5] is an online tool that calculates the risk for diabetes and complications associated with it. Diabetes PHD is based on a math model called Archimedes [6] that represents the anatomy, physiology and pathology related to diabetes and its complications. In the virtual world of Archimedes, every element corresponds to the same elements in the real world, one-to-one. The model is populated with thousands of simulated people, all of whom are living simulated lives, sometimes developing simulated diabetes and/or its complications.

The user has to set basic information (age, weight, gender, etc.), basic family health history, blood pressure, cholesterol levels, HbA1c, Fasting Plasma Glucose, health history and current medications related to diabetes.

The Diabetes PHD calculator gives percentages of risk for diabetes (if the person doesn't have already) and 5 complications of diabetes (type 1 and 2). Probabilities are for the next 30 years and are displayed as graphs. The report also provides an accurate picture of how the individual can alter those risks with lifestyle modification actions such as losing weight, quitting smoking, or reducing blood pressure or cholesterol levels.

3.2 Qrisk2 Cardiovascular Risk Score

Qrisk2 [7] is a cardiovascular disease risk calculator which is designed to identify people at high risk of developing CVD and need to be recalled and assessed in more detail in order to reduce their risk of developing CVD. The Qrisk2 score estimates the risk of a person developing CVD over the next 10 years.

Qrisk is using a cohort of 1.28 million patients without evidence of diabetes mellitus or cardiovascular disease. Patients were followed up for >5 years, looking for the first development of cardiovascular disease as an endpoint. Qrisk2 has been specifically developed by doctors and academics for use in the United Kingdom.

The Qrisk2 calculator uses the following parameters (if known - missing values are calculated by a complex averaging procedure called multiple imputations): patient age (35-74), patient gender, current smoker, family history, existing treatment with blood pressure agent, postcode related Townsend score (an area measure of deprivation), body mass index, systolic blood pressure, total and HDL cholesterol, self-assigned ethnicity, rheumatoid arthritis, chronic kidney disease, atrial fibrillation.

The output of the calculator is a score (percentage) of probability to have cardiovascular disease the next 10 year. The calculator also gives the score of a typical person (good reference) with the same age, sex, and ethnicity and a relative risk (patient's risk divided by the typical risk).

3.3 Framingham Heart Study

The Framingham Heart Study [8] is a risk predictor for the risk of various cardiovascular disease outcomes in different time horizons and it is available as score sheets or direct risk functions. In the Framingham Heart study there are six groups of participants: Original Cohort, Offspring Cohort, Third Generation Cohort, New Offspring Spouse Cohort, Omni Generation 1 Cohort and Omni Generation 2 Cohort.

The inputs for a risk prediction about stroke were defined as follows: systolic blood pressure, diabetes, history of diabetes, smoking and if yes how many cigarettes per day, CVD, history of myocardial infarction, angina pectoris, coronary insufficiency, intermittent claudication or congestive heart failure, atrial fibrillation, history of atrial fibrillation, left ventricular hypertrophy on electrocardiogram.

The output of the model is probability of stroke within 10 years and heart disease for 10 or 30 years.

3.4 Risk Score Calculator

The risk score calculator [9] is a score which is derived from data on 47,088 men and women who participated in eight randomized controlled trials of drug treatment for high blood pressure in Europe and North America. Average follow-up was over 5 years and 1,639 patients died of cardiovascular disease (1,031 coronary heart disease, 371 stroke and 237 other). Two of these trials were on 21,750 British subjects and their data have been used to give a country-specific probability of cardiovascular death linked to a person's risk score.

Inputs for the risk score calculator are: Age, Sex, Current cigarette smoker, Systolic blood pressure, Total cholesterol, Creatine, Height, Has diabetes, Has left ventricular hypertrophy, Had myocardial infarction and Had stroke.

The output consists in (a) the risk of death due to a cardiovascular cause in the next 5 years, (b) a graph with the risk of cardiovascular mortality, and (c) a graph with the distribution of risk scores for the specific sex.

3.5 UKPDS Risk Engine

The UKPDS Risk Engine [10] is a type 2 diabetes specific risk calculator based on 53,000 patients' years of data from the UK Prospective Diabetes Study.

The UKPDS risk engine calculates complications of type 2 diabetes based on age, sex, ethnicity, smoking status, presence or absence of atrial fibrillation, levels of HbA1c, systolic blood pressure, total cholesterol and HDL cholesterol.

The UKPDS Risk Engine provides risk estimates and 95% confidence intervals, in individuals with type 2 diabetes not known to have heart disease, for:

- Non-fatal and fatal coronary heart disease
- Non-fatal and fatal stroke

The UKPDS Risk Engine is intended primarily for use by health care professionals to assist in the management of people with type 2 diabetes.

3.6 HARP Risk Calculator

HARP risk calculator [11] is based on the extensive work done with the Westbay diabetes project. The calculator aims to determine the risk of people with chronic or complex care needs presenting to hospital for treatment in the following 12 months.. The risk screen is based on presenting clinical symptoms, service access profile,

self-management, and psycho-social issues. This screening categorizes a person into one of four risk categories: low, medium, high and urgent.

HARP risk calculator developed to measure predictable level of risk for diabetes related complications in the next 12 months.

4 Discussion

During the last decades diabetes and its complications have been intensively studied and clinical trials have been designed in order to understand and handle better the therapy of diabetes and its complications. Table 1 gives a summary of the available risk assessment tools and applications for diabetes complications with their major features. There are several remarks that have to be done related to the use of these risk assessment tools. As we can see from table 1 all the risk assessment applications except diabetes PHD are based on big studies such as UKPDS, Qrisk or DCCT. These studies measure and store a large number of risk factors for a long period for every patient. DCCT and EDIC studies were conducted from 1983 to 1993. UKPDS study ran from 1977 to 1991 in 23 UK clinical sites and Qrisk study started in 1995. Having in mind the evolution in clinical sensors and in electronic health care records someone could claim that the data of these studies is obsolete. Measurements for specific risk factors that could not be measured twenty years ago now are available with specialized sensors and sensor accuracy and reliability has been significantly increased. Furthermore, the normal values for various risk factors, such as blood pressure, have been revised during the years.

Table 1. A summary of the available risk assessment applications (web based or standalone) for diabetes complications

	Diabetes PHD	Qrisk 2	Framingham Heart Study	Risk Score calculator	UKPDS Risk Engine	HARP Risk Calculator
Study/Training of model	Archimedes simulator	2.3 million patients	Framingham Study cohort	47,088 patients from Europe(UK) and North America.	UK Prospective Diabetes Study	Westbay diabetes project
Diabetes Type	Type I & II	with & without diabetes	with & without diabetes		Type II	
Region	No	UK	USA	UK & USA	UK	No
Type of application	web page	web page	Online calculators and Excel spreadsheets.	web page	Standalone application	Forms with a final score
Num. of attributes needed	more than 20	16	depends on the disease	11	10	40
Prediction	Diabetes, Heart attack, stroke, kidney failure eye problems, foot problems	diabetes, heart disease, stroke for the next 10 years	stroke, heart diseases.	country-specific probability of cardiovascular death	heart disease, coronary heart disease, stroke	risk for diabetes related complications in the next 12 months.

Another limitation is the close relation of diabetes and its complications with the geographical location of the patient. Environmental characteristics such as special diet and lifestyle characteristics such as socioeconomic status of the patients' population are strongly associated with diabetes mellitus [12]. For that reason Qrisk2 and UKPDS risk engine are risk calculators focused on the United Kingdom population.

Diabetes PHD seem to overcome theses limitations in the sense that it is based on Archimedes model which is a large-scale simulation model of human physiology and health care systems. Of course the use of virtual data as cohort is a limitation itself.

5 The REACTION Project

The REACTION project aims to research and develop an intelligent service platform that can provide professional, remote monitoring and therapy management to diabetes patients in different healthcare regimes across Europe. A range of REACTION applications will be developed mainly targeting insulin-dependent type 1 patients.

Part of this effort consists in reviewing, developing and implementing tools able to provide long term risk assessment evaluations based on patient's current health state and history. The tools will allow for integration between instantaneously measured data from sensors, historic data from EPR, statistical data from stratification studies, statistical database and evidence based case management repositories.

A continuous update and calibration with independent off-line measurements of relevant biomarkers and diagnostic tools is possible. For the developed tools, emphasis will be put on usability and clearness of personalized feedback. This will allow easy and readily available risk assessment tool to both clinicians and patients, which can be customized according to user needs and preferences.

Last but not least, REACTION decision support services will undergo a preliminary validation phase within the clinical sites involved into the project. The relatively limited project's duration does not allow an exact evaluation of the accuracy of the predictive models: assessing the validity of predictions related to events that can arise within a time horizon of thirty years requires ad hoc longitudinal studies, that are out of the scope of the REACTION project. However, our preliminary validation phase will provide precious information about the impact that decision support tools can have on the daily clinical management of diabetes patients.

6 Conclusion

The present work introduced and discussed the main clinical studies for diabetes risk factors. Moreover, the risk assessment tools developed on the basis of the data collected during these studies were reviewed as well. Finally, we described a new EU project, REACTION, that will develop and integrate a series of risk assessment models for diabetes complications.

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