

HYPO RESOLVE

Hypoglycaemia - REdefining SOLutions for better liVEs

Executive Summary 3rd Project Period

Period covered: 01/05/2020 to 30/04/2021

Coordinator: Dr. Bastiaan de Galan, Radboud university medical center/STICHTING KATHOLIEKE UNIVERSITEIT

Project Leader: Dr. Stephen Gough, NovoNordisk A/S

Contact: Bastiaan.deGalan@radboudumc.nl



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Diabetes is a major non-communicable threat to global health that imposes an increasing burden on global health care resources. Lowering glucose levels to those in the non-diabetic range reduces the risk of vascular complications and mortality. However, treatment with insulin and insulin secretagogues, which stimulate insulin secretion independent of the glucose level, is associated with increased risk of hypoglycaemia (low blood sugar). On average, hypoglycaemic events occur at a weekly to monthly basis in people with type 1 and type 2 diabetes treated with insulin, respectively. Hypoglycaemia causes profound physical and mental stress, and is associated with adverse clinical consequences, including death, psychological stress, poor quality of life and elevated costs.

However, although the adverse clinical, psychological and health-economic consequences of severe hypoglycaemia (in which cognitive dysfunction requires assistance from another person for recovery) are reasonably well described, this is much less clear for so-called 'non-severe' hypoglycaemia, in which the person maintains cognitive function sufficient for self-help. It also remains to be established which underlying mechanism(s) explain the association between hypoglycaemia and cardiovascular events and below which glucose level hypoglycaemia is associated with adverse outcomes. Finally, the pathophysiology underlying impaired awareness of hypoglycaemia has not been fully explained and it is unclear how hypoglycaemia detected by continuous glucose monitoring (CGM) should be considered in clinical practice or in trials. Clarifying these uncertainties is fundamental in providing the classification of hypoglycaemia in diabetes with sufficient evidence base.

The overall aim of the current project is to reduce the burden and consequences of hypoglycaemia in people with diabetes by increasing our understanding of hypoglycaemia. This objective will be achieved by answering the abovementioned questions using a comprehensive multi-layered approach, in which academia, industry and people affected by or living with diabetes closely collaborate in a non-competitive way.

Radboud university medical center/STICHTING KATHOLIEKE UNIVERSITEIT - KING'S COLLEGE LONDON - MEDIZINISCHE UNIVERSITAT GRAZ - THE CHANCELLOR MASTERS AND SCHOLARS OF THE UNIVERSITY OF CAMBRIDGE - CENTRE HOSPITALIER UNIVERSITAIRE MONTPELLIER - SYDDANSK UNIVERSITET - UNIVERSITE DE LAUSANNE - THE UNIVERSITY OF SHEFFIELD - REGION HOVEDSTADEN - UNIVERSITY OF DUNDEE - EURICE EUROPEAN RESEARCH AND PROJECT OFFICE GMBH - SIB INSTITUT SUISSE DE BIOINFORMATIQUE - UNIVERSITA DEGLI STUDI DI PADOVA - THE UNIVERSITY OF EDINBURGH - NOVO NORDISK A/S - Eli Lilly and Company Limited - ABBOTT DIABETES CARE - MEDTRONIC INTERNATIONAL TRADING SARL - JDRF INTERNATIONAL - FEDERATION INTERNATIONALE DU DIABETE - UNITIO INC - THE LEONA M. AND HARRY B. HELMSLEY CHARITABLE TRUST

The work has been distributed over a total of eight different work packages. With respect to project management, a governance structure has been set in place to provide support for individual scientists, monitor progress and coordinate project activities. A website, twitter account and dissemination toolkit have been established to create awareness of the project's mission, vision and progress. This year, we published an animated clip that explains the project in three minutes for a general audience. Also, podcast videos between WP leads and members from the Patient Advisory Committee (PAC) have been recorded. A key part of the project is the construction of the large, secure and sustainable Hypo-RESOLVE database with data on hypoglycaemia and other clinical parameters from 98 individual clinical trials involving >60,000 people with diabetes treated with insulin, including 16 trials with data on CGM. A statistical analysis plan, based on a Bayesian inferential framework, has been established and iteratively refined to analyse these data, one pertaining on prediction of hypoglycaemia, and another on the consequences of hypoglycaemia. Stakeholder meetings have been held to discuss the classification of hypoglycaemia. Human and animal experimental studies are being conducted to uncover mechanisms underlying cardiovascular and other clinical consequences of hypoglycaemia. A total of 94 people with type 1 or type 2 diabetes or without diabetes participated in hyperinsulinaemic hypoglycaemic clamp studies to examine the effect of (experimental) hypoglycaemia on cardiac and cognitive function and on inflammatory and epigenetic parameters to explain the association between hypoglycaemia and vascular outcomes. Also, animal models have been developed to study new hypoglycaemia sensing pathways and how to quantify symptoms of hypoglycaemia in animals. An animal study showing that cold exposure as novel stimulus may dishabituate hypoglycaemia-induced suppression of counterregulatory responses supports the notion that impaired awareness of hypoglycaemia follows from habituation to recurrent hypoglycaemia. Using some in-house datasets, models have been developed for carb counting error, and meal and snack timing. Sensitivity analysis have been initiated to factor in delays to mealtime boluses. The study protocol for the multi-centre clinical study, Hypo-METRICS, which will examine the clinical relevance and consequences of CGM-detected low glucose values among 600 patients with type 1 or insulin-treated type 2 diabetes, has been approved by all eight participating centres. An app for smart phones has been developed to capture and monitor patient-reported outcomes (PROs) related to hypoglycaemia throughout the 10 weeks of follow-up in this study and recruitment has started. A systematic review to determine the impact of hypoglycaemia on quality of life in adults with type 1 diabetes has been published and others investigating its impact on quality of life in adults with type 2 diabetes, children with type 1 diabetes and family members and on its effect on cognitive function and academic performance are underway. The (online) qualitative study to explore the facets of quality of life affected by hypoglycaemia in people with diabetes and their family members has been conducted and the larger quantitative study to quantify these effects in more detail is currently recruiting. Finally, a review on the definition and classification of hypoglycaemia in guidelines and consensus reports shows a very large variety in how hypoglycaemia is defined, in part due to newer glucose measurement technology. A systematic review on seven 'hypoglycaemia-specific' PROs currently used in studies involving hypoglycaemia, revealed the content and structural validity to be inconsistent or otherwise unsatisfactory, justifying the need for a new PRO. Data that come out of the Hypo-METRICS study will be used to develop a hypoglycaemia-specific PRO for future studies. A stakeholder meeting has been organised to establish and maintain a dialogue with key regulators, HTA body representatives and other key stakeholders. Also, the dialogue with key regulators was further advanced via an Innovation Task Force (ITF) meeting with the European Medicines Agency (EMA) and by obtaining EMA Qualification Advice for the development of the new PRO.

Expected final results and impact

Data coming out of this project will advance our understanding of predictors for and clinical, psychological and health-economic consequences of hypoglycaemia. The project will also elucidate mechanism(s) underlying the association of hypoglycaemia with long-term (cardiovascular) consequences and the clinical relevance of low interstitial glucose values (as measured by CGM). These data are expected to provide the evidence currently missing for refining the classification of hypoglycaemia in people with diabetes at risk of medication-associated hypoglycaemia. Adoption of the refined classification in relevant guidelines will have significant impact on the diabetes community, including people with diabetes, health care professionals, regulators, scientists and industry, and for adoption of hypoglycaemia as an efficacy outcome for future clinical trials. Also, the new hypoglycaemia-specific PRO will be made available for use in clinical trials.

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