HYPO RESOLVE

Hypoglycaemia - REdefining SOLutions for better liVEs

Executive Summary
1st Project Period

Period covered: 01/05/2018 to 30/04/2019

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This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 777460. The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA and T1D Exchange, JDRF, International Diabetes Federation (IDF) and The Leona M. and Harry B. Helmsley Charitable Trust.

Context and Objectives

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 (secretagogues) is associated with increased risk of hypoglycaemia (low blood sugar), which on average occurs at a weekly to monthly basis in people with type 1 and type 2 diabetes, respectively. Hypoglycaemia causes profound physical and mental stress, and is associated with adverse clinical and psychological consequences 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 harm. Finally, the pathophysiology underlying impaired awareness of hypoglycaemia has not been fully explained and it is unclear how hypoglycaemia detected by CGM (continuous glucose monitoring) should be considered. 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.

Partners

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 - SANOFI-AVENTIS DEUTSCHLAND GMBH - ABBOTT DIABETES CARE - MEDTRONIC INTERNATIONAL TRADING SARL - JDRF INTERNATIONAL - FEDERATION INTERNATIONALE DU DIABETE - UNITIO INC - THE LEONA M. AND HARRY B. HELMSLEY CHARITABLE TRUST

Scientific Results

The work has been distributed over a total of 8 different work packages.

With respect to project management (Work Package 1) 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.

Animal models have been developed to study new hypoglycaemia sensing pathways as well as symptomatic awareness of hypoglycaemia (Work Package 2). The protocol to examine the effect of hypoglycaemia on inflammatory, epigenetic and related consequences of hypoglycaemia in humans with or without (type 1/type 2) diabetes has been finalised and approved by institutional review boards in the Netherlands and Denmark, where these experiments will be conducted.

For the creation of a large, sustainable Hypo-RESOLVE database (Work Package 3), secure data transfer procedures have been set up to transfer clinical trial data to the Hypo-RESOLVE server. Prioritisation for data transfer has been given to clinical trials with the most standardised format (e.g. CDISC) as well as to those that are the most recent, included the largest number of participants and have longest follow-up. Thus far, de-identification of trials and subsequent standardisation and harmonisation of clinical trial and CGM data have been completed for demographics and vital signs for 36 trials and for glucose measurements for 19 trials (out of >100 trials). Transfer of data on laboratory measurements, adverse events, medication and patient-reported outcomes (PROs) from these trials is ongoing.

Systematic reviews are being conducted to determine with greater precision the current status of known predictors and known consequences of hypoglycaemia (Work Package 4). Two stakeholders meetings have been held to discuss the classification of hypoglycaemia. A statistical analysis plan is being developed and tested to optimise future analysis of data of the Hypo-RESOLVE database (Work Package 4), one pertaining on the risk factors of hypoglycaemia, and another on the consequences of hypoglycaemia. A Bayesian posterior distribution method has been tested as the best fit to model risk factors for the prediction of hypoglycaemia. Similarly, a data analysis plan to evaluate the link between CGM-detected low glucose values and documented (severe) hypoglycaemia in the Hypo-RESOLVE database is in development (Work Package 5).

A systematic literature review to map hypoglycaemia detection techniques and identify gaps that have not been addressed is underway. Preparations for the simulation framework for in-silico analysis on behavioural risk factors for hypoglycaemia have been initiated. The study protocol for the multicentre clinical study, which will run among >600 patients, on the clinical relevance and consequences of asymptomatic, sensor-documented low glucose values is under development, and project managers and a data analyst have been appointed. An app has been developed for ecological momentary assessments (EMAs) to capture PROs throughout the clinical study. Search strings and other preparations have been set up for the series of systematic reviews to determine the impact of hypoglycaemia on quality of life in people with diabetes and family members as well as on cognitive function and academic performance in people with diabetes (Work Package 6).

A search strategy has been developed to identify a total of 233 potentially relevant PROs, which could be classified as diabetes-specific (n=123), treatment related (11), hypoglycaemia-specific (6), related to glucose monitoring (4), and uncategorised (87) or generic (81). Work is currently ongoing to rate these PROs (except those labelled 'generic') using COSMIN (COnsensus-based Standards for the selection of health Measurement INstruments) guidelines (Work Package 7).

A protocol is under development for developing new or refining existing PRO instruments. As a first step towards establishing and maintaining a dialogue with stakeholders, key regulators, HTA body representatives and other key stakeholders were identified and approached for participating in the first Hypo-RESOLVE

Stakeholder meeting, which was held on 30 September 2018 in Berlin (Work Package 8). Also, a systematic review protocol was written to analyse definitions and management of hypoglycaemia among existing guidelines. A total of 54 guidelines and 32 position statements (in >10 different languages) were retrieved for inclusion in this review, the processing of which is now in progress.

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, as well as underlying mechanisms and the link with and impact 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 using medication potentially causing 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. We feel that such a widely agreed on classification is needed to include hypoglycaemia as an efficacy outcome for future clinical trials.

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