Validation of a virtual patient and virtual trials method for accurate prediction of TGC protocol performance

F Suhaimi[1]; AJ Le Compte[1]; S Penning[2]; CG Pretty[1]; J-C Preiser[3]; GM Shaw[3]; T Desaive[2]; JG Chase[1];

1: Univ of Canterbury, Christchurch, NZ
2: Univ of Liege, Belgium
3: Erasmus Hospital, Brussels, Belgium
4: Christchurch Hospital, Christchurch, NZ

Introduction: Effective tight glycemic control (TGC) can improve outcomes, but is difficult to achieve. *In silico* virtual patients and trials offer significant advantages in cost, time and safety for designing effective TGC protocols. However, no such method has been fully validated. This study tests 2 matched cohorts from the Glucontrol trial treated with different protocols. The goal is to validate the ability of *in-silico* virtual patient models and methods to accurately predict patient-specific and clinical trial glycemic outcomes.

Method: The analysis uses records for a 211 patient subset of the Glucontrol trial (Liege, Belgium). Glucontrol-A (N=142) targeted 4.4-6.1mmol/L and Glucontrol-B (N=69) targeted 7.8-10.0mmol/L. Cohorts were matched by APACHE II score, age and sex ($p>0.3$). The Glucontrol A cohort was slightly older ($p=0.04$). Virtual patients are created by fitting a clinically validated model to the data, yielding time varying insulin sensitivity profiles (SI(t)) that create *in-silico* virtual patients.

Model fit and intra-patient (forward) prediction are used to validate individual *in-silico* virtual patients. Self-validation (tests A protocol on Group A virtual patients; and B protocol on B virtual patients) and cross-validation (tests A protocol on Group B virtual patients; and B protocol on A virtual patients) assess ability to predict a clinical trial result.

Results: Model fit errors were small (<0.25%) for Group A, Group B and the entire cohort (A+B), indicating model fitness. Median prediction errors were: 4.3, 2.8 and 3.5% for Group A, Group B and (A+B), indicating individual virtual patients were accurate representations of real patients. Self and cross validation results were within 1-10% of the clinical data for both Group A and Group B. Self validation indicated clinically insignificant model and compliance errors. Cross validation clearly showed that the virtual patients enabled by identified patient-specific SI(t) profiles can accurately predict the performance of TGC protocols different from those used to create the virtual patients.

Conclusions: This study validates these virtual patients and in silico virtual trial methods, and clearly shows they can accurately simulate, in advance, the clinical results of a TGC protocol, enabling rapid in silico protocol design and optimization. It is the first rigorous validation of a virtual *in-silico* patient and virtual trials methodology.