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Dapagliflozin pharmacokinetics is similar in adults with type 1 and type 2 diabetes mellitus

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Abstract

Aim: Dapagliflozin improves glycaemic control in patients with type 2 diabetes mellitus (T2DM) and is approved in European and Japanese patients with type 1 diabetes mellitus (T1DM) with inadequate glycaemic control. The objectives of this work were to characterise the dapagliflozin pharmacokinetics (PK) in patients with T1DM, assess the influence of covariates on dapagliflozin PK, and compare dapagliflozin systemic exposure between patients with T1DM and T2DM. Methods: Population PK analysis was performed using a non-linear mixed-effect modelling approach. The analysis included 5,793 dapagliflozin plasma concentrations from 1,150 adult patients with T1DM, collected from one phase 2 (NCT01498185) and two phase 3 studies (DEPICT-1, NCT02268214; DEPICT-2, NCT02460978). Covariate effects were investigated using stepwise covariate modelling. Model-derived area under the concentration-time curve (AUC) was compared with AUC in patients with T2DM. Results: The final two-compartmental model adequately described the dapagliflozin concentrations in patients with T1DM. The estimated apparent clearance was 20.5 L/h. Model-predicted systemic exposure for 5 mg and 10 mg of dapagliflozin indicated dose-proportionality and was comparable between patients with T1DM and T2DM. The identified covariate relationships showed that patients with better renal function (measured as estimated glomerular filtration rate), males, and heavier patients had lower dapagliflozin systemic exposure. Among the covariates studied, no covariates affected dapagliflozin systemic exposure to a clinically relevant extent. Conclusions: Dapagliflozin PK in patients with T1DM was adequately described by the population PK model and no clinically relevant covariates were identified. Dapagliflozin systemic exposure was comparable between patients with T1DM and T2DM. NCT01498185, NCT02268214, NCT02460978

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Principal investigator statement: This was a pure population pharmacokinetic (PK) analysis of one Phase 2 and two Phase 3 international studies. Consequently, none of the principal investigators have contributed to the sample collection design, PK analysis plan, data analysis and manuscript preparation. Therefore, principal investigators have not been included as co-authors in this manuscript.

Running head: Similar dapagliflozin PK in T1DM & T2DM

Keywords: dapagliflozin, diabetes, pharmacokinetics

What is already known about this subject?

Dapagliflozin is a potent sodium-glucose cotransporter type 2 inhibitor used for the treatment of type 2 diabetes mellitus (T2DM) worldwide, type 1 diabetes mellitus (T1DM) currently in Europe and Japan, and heart failure with reduced ejection fraction in USA and Europe.

What this study adds?

- PK of dapagliflozin in patients with T1DM was characterized employing a population PK approach using phase 2 and phase 3 clinical data
- None of the identified covariates affected systemic dapagliflozin exposure to a clinically relevant extent
- Systemic exposure of dapagliflozin was comparable in patients with T1DM and T2DM

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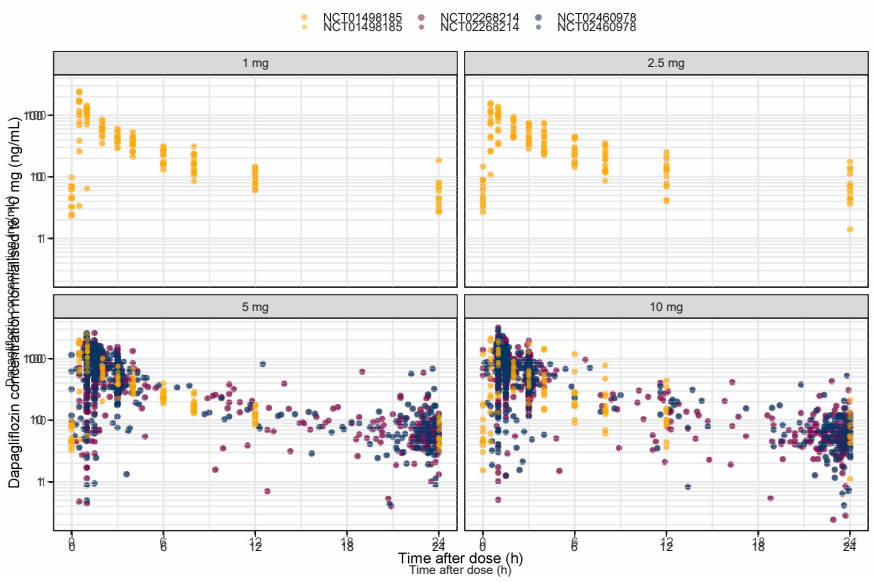

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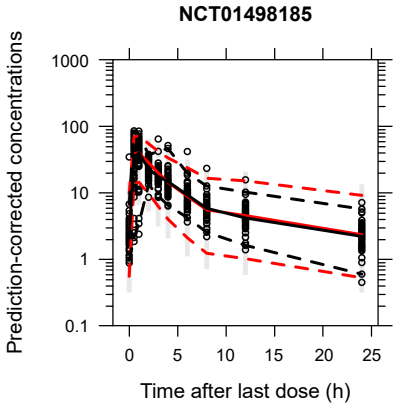

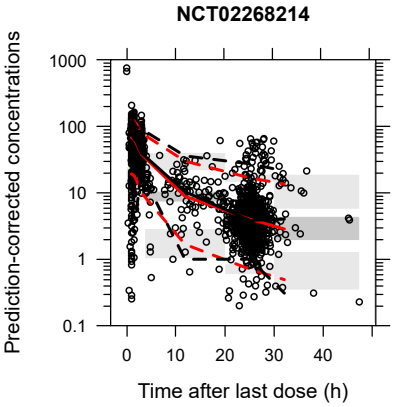

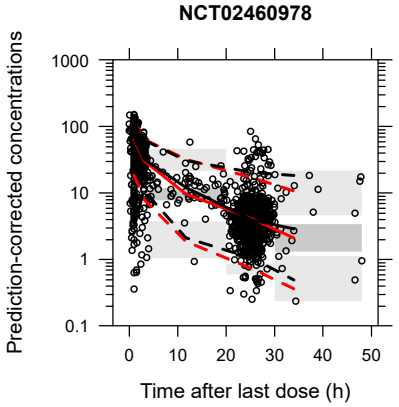

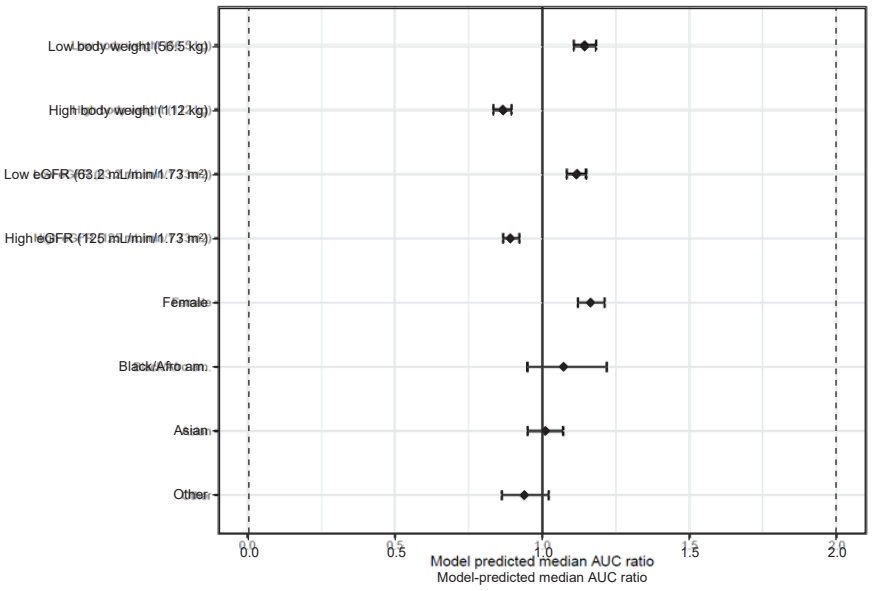

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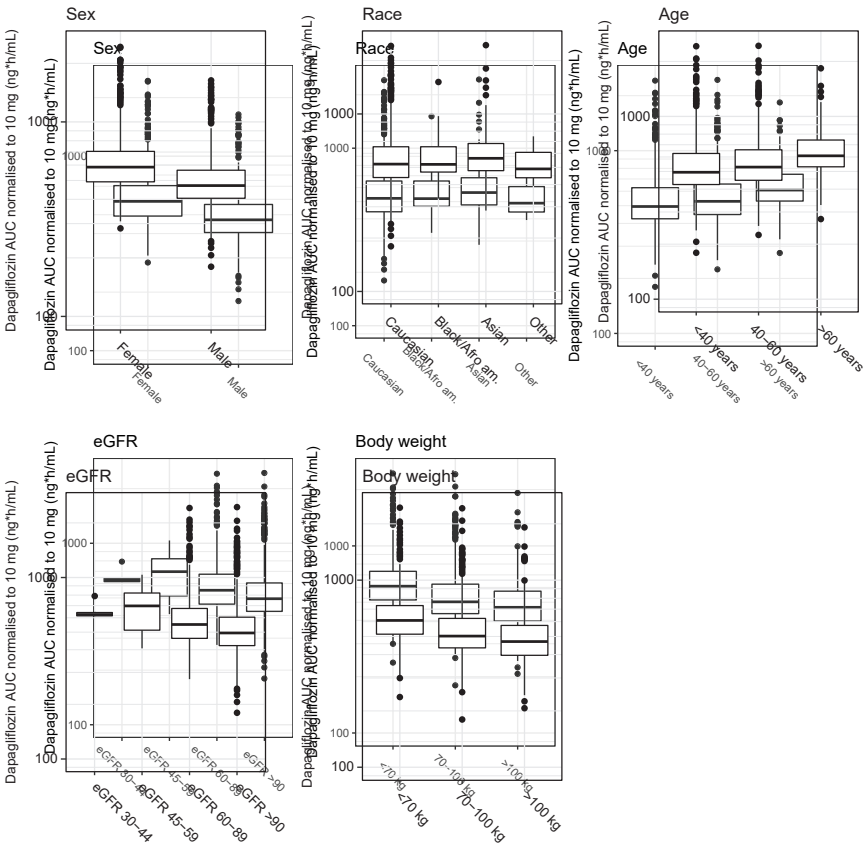

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