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Optimizing Simvastatin Dosing in Patients Post-gastric Bypass Surgery Using a Population PK/PD Link Approach

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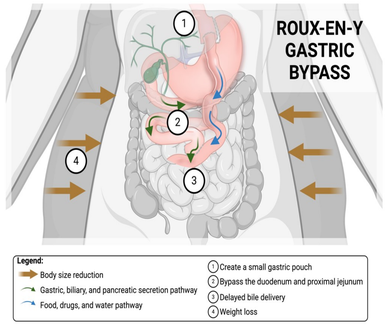
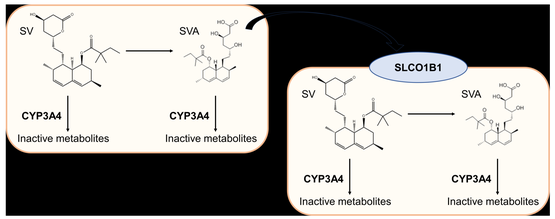
INTRODUCTION AND OBJECTIVES





Our primary aim was to assess the impact of gastric bypass surgery on the PK of simvastatin lactone (SV) and its active metabolite, simvastatin hydroxy acid (SVA). Ultimately, we aimed to optimize dosing for this understudied population by employing a population pharmacokinetic–pharmacodynamic link approach

METHODS

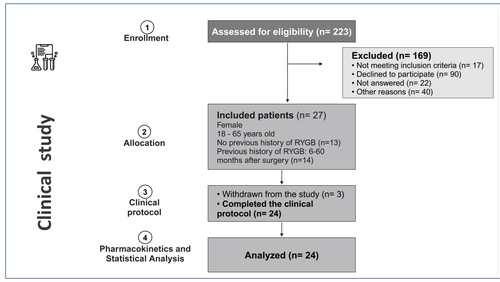
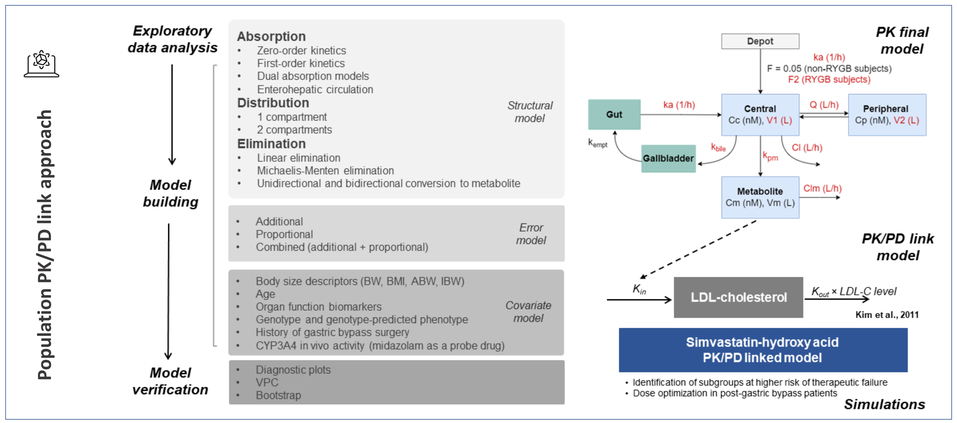


Table 1. Demographic and clinical data of the investigated subjects (n=24)

Clinical data	Average ± SD [min-max]
Age (years)	42.45 ± 8.2 [26-58]
Sex (% de females)	100
History of gastric bypass surgery	
No surgery (n, %)	10 (41.67%)
Previous RYGB surgery (n, %)	14 (58.33%)
BMI (kg/m^2)	
All participants	35.3 ± 11 [23.73-63.02]
No surgery	46.4 ± 8.5 [44.2-63.02]
Previous RYGB surgery	28 ± 2.7 [23.73-32.4]
eGFR (mL/min/1.73 m^2)	106.36 ± 8.47 [86.3-123.55]
Serum albumin (g/dL)	4.11 ± 0.26 [3.72-4.68]



RESULTS

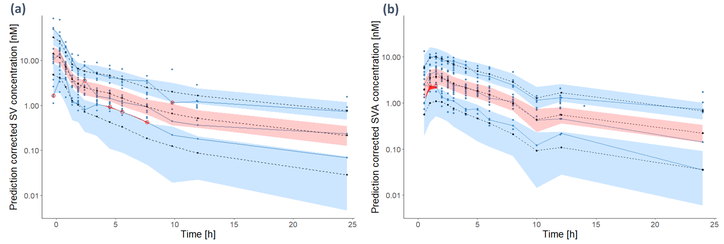


Figure 1. Diagnostic plots showing the prediction corrected visual predictive check after 1000 simulations for SV (a) and SVA (b). SV: simvastatin lactone; SVA: simvastatin acid.

- **Model predictions align closely with observed data for both SV and SVA**
- **There is a 40% reduction in oral bioavailability in patients post-gastric bypass surgery**
- **Subjects with *SLCO1B1* 521TC genotype showed reduced clearance of SVA compared to homozygous wild-type carries (521TT)**

Table 2. Population pharmacokinetic model parameter estimates for the parent-metabolite model for simvastatin and simvastatin acid

Parameters (unit)	Population Estimates [% RSE]	Bootstrap Analysis* median [95% CI]
F	0.05 [fixed]	0.05 [fixed]
F2	0.03 [0.067]	0.033 [0.021-0.050]
ka (h^{-1})	0.84 [16.2]	0.87 [0.59-2.58]
V1 (L/h)	47.63 [21.7]	55.32 [28.23-96.77]
Cl (L)	18.73 [60.7]	16.04 [0.06-56.45]
Q (L)	77.41 [21.2]	87.96 [60.39-127.38]
V2 (L/h)	676.64 [29.1]	863.30 [347.48-2354.12]
V_m (L)	59 [fixed]	59 [fixed]
Cl_m (L/h)	60.44 [19.6]	59.84 [37.19-100]
SLCO1B1_TC on CL_m	-0.77 [38]	-0.70 [(-1.57)-(-0.08)]
SLCO1B1_CC on CL_m	-1.29 [29.2]	-1.34 [(-1.92)-(-0.03)]
Kpm (h^{-1})	0.66 [21.5]	0.59 [0.34-0.88]
K_{bile} (h^{-1})	0.56 [0.083]	0.49 [0.23-0.91]
K_{empt} (h^{-1})	15 [fixed]	15 [fixed]
T_{gap} (h)	3.43 [10.5]	3.49 [2.7-4.77]
Random effects [ω]		
ka	0.46 [33.9]	0.48 [0.21-1.34]
V1	0.46 [28.7]	0.39 [0.09-0.69]
Cl	1.42 [38.2]	1.33 [0.71-2.65]
Q	0.7 [25.5]	0.65 [0.24-1.04]
V2	0.46 [57.9]	0.52 [0.15-1.10]
V_m	0.64 [fixed]	0.64 [fixed]
Cl_m	0.37 [26.4]	0.28 [0.05-0.51]
Kpm	0.32 [66.8]	0.30 [0.10-0.63]
T_{gap}	0.35 [fixed]	0.35 [fixed]
Residual Error Model [ε]		
b2 (SVA)	0.42 [6.03]	0.42 [0.37-0.46]
b1 (SV)	0.41 [6.65]	0.41 [0.36-0.45]

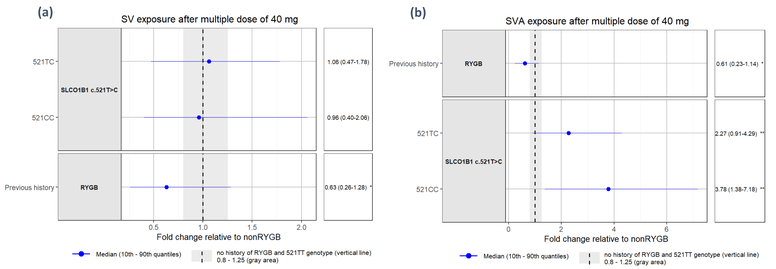


Figure 2. Effect of covariates on SV and SVA exposure after multiple dose of 40 mg. (a): $AUC_{0-\tau}$ of SV; (b): $AUC_{0-\tau}$ of SVA. SV: simvastatin; SVA: simvastatin acid; RYGB: gastric-bypass. *Mann-Whitney test (p<0.05)

- **Patients post-gastric bypass have a decrease in the AUC_{0-tau} by approximately 40%**
- **There was a 98% increase in the AUC_{0-tau} for individuals with the 521TC genotype and a 264% increase for those with the genotype 521CC**

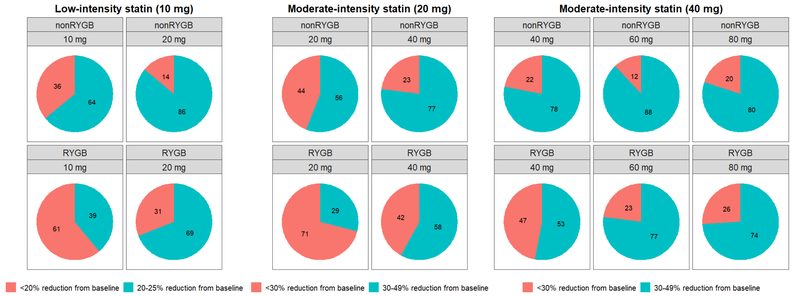


Figure 3. PK/PD simulations to compare the percentage of subjects achieving certain goals in LDL-C baseline reductions in virtual subjects genotyped as *SLCO1B1* 521TT. For low-intensity statin (a), responders were classified as achieving a reduction of 20%-25%; for moderate-intensity statin (b and c), responders were classified as achieving a reduction of 30%-49%. Data are shown as percentages of responders (green) and non-responders (orange).

- **For low-intensity statin patients: an increase in the dose from 10 to 20 mg in post-gastric bypass patients will maintain a comparable response to that of non-operated subjects.**
- **For moderate-intensity statin: increasing the dose to 40 or 60 mg or adding a non-statin medication in post-gastric bypass will result in similar therapeutic outcomes.**

CONCLUSIONS

- Gastric bypass surgery reduces oral bioavailability and exposure to SV by approximately 40%.
- Individuals post-RYGB exhibit diminished exposure to SV and may benefit from increasing the dose or adjunctive therapy with non-statin drugs to attain equivalent responses and mitigate potential adverse events.

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