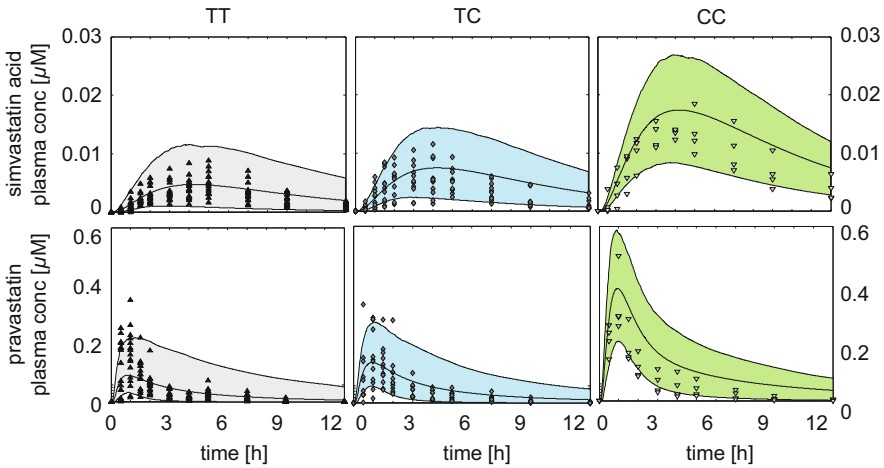

Fig. 9 Plasma concentration-time profiles for simvastatin and pravastatin were simulated for populations stratified by OATP1B1 genotype and compared to experimental data (modified from Lippert et al. 2012)

rates and enzyme and transport protein expression levels), the interindividual variability of plasma concentrations can also be predicted accurately (Fig. 9).

The successful prediction of PK in heterozygous subjects and the correct simulation of PK variability in stratified populations of subjects treated with pravastatin and simvastatin indicate the correct representation of the most relevant PK properties of these statins by the PBPK models.

The CC genotype was linked to an increased risk to develop a myopathy under simvastatin treatment (Link et al. 2008). This is in line with the increased exposure in plasma of patients with the CC genotype (Figs. 7 and 8) and a direct result of the relevance of OATP1B1 for hepatic uptake and clearance from the body (Niemi et al. 2011). The myopathy risk is, however, not directly linked to plasma concentrations of statins. Pravastatin exposure is significantly higher than simvastatin exposure and naïve correction for potency cannot reconcile the differences in myopathy incidence rates alone.

To bridge from well-represented plasma PK behavior to safety events resulting from muscle cell degradation, the PBPK model can be used to simulate mean muscle concentrations obtained in populations stratified by OATP1B1 genotype because muscle is represented explicitly in the PBPK model. The ratio between these predicted muscle concentrations and in vitro potency data (half maximal inhibitory concentrations determined with embryonic rhabdomyosarcoma cells; Kobayashi et al. 2008) provides a toxicodynamic measure. Figure 10 shows the resulting predicted incidence rates for ratio between muscle concentrations and the inhibitory concentration of simvastatin.

A comparison of simulated incidence rates of high toxicodynamic marker levels with clinical myopathy incidence rates in the SEARCH study (Link et al. 2008)