Abstract: Role of the gut microbiome for the cholesterol lowering effect of atorvastatin

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Background and Aims
Statins show interindividual differences in the extent of low-density lipoprotein cholesterol (LDL-C) reduction. The mechanisms of this interindividual variation are not fully understood. Here, we examined the potential role of the gut microbiome for the LDL-C lowering property of atorvastatin.

Methods
Mice (C57BL/6) with either intact (conventional mice, CONV, n=24) or with antibiotic depleted gut microbiome (gnotobiotic, n=16), were put on standard chow diet (SCD) (n=11) or high fat diet (HFD) (n=29) for 6 weeks. During the last 4 weeks atorvastatin (Ator, 10mg/kg body weight/day) or control vehicle was orally applied via gavage. Blood levels of LDL-C and glucose and body weight after 6 weeks of treatment were compared between the groups. Expression of genes involved in hepatic and intestinal cholesterol-metabolism were examined. Faeces of CONV mice were analyzed for alteration of the gut microbiota profile upon atorvastatin treatment using 16S rRNA qPCR.

Results
HFD fed mice with intact gut microbiome showed significantly increased blood LDL-C levels as compared to SCD (HFD: 36.8±1.4 mg/dl vs. SCD: 22.0±1.8 mg/dl; P<0.01). Bodyweight gain or blood glucose levels after HFD were not significantly different between CONV and gnotobiotic mice. While in CONV mice atorvastatin significantly reduced LDL-C levels after HFD, in gnotobiotic mice the LDL-C lowering effect of atorvastatin was attenuated (CONV+HFD+Ator: 31.0±1.8 mg/dl vs. gnotobiotic mice+HFD+Ator: 46.4±3 mg/dl; P<0.01). The expression of genes involved in hepatic cholesterol synthesis was not significantly altered in gnotobiotic mice as compared to CONV mice. In CONV mice HFD decreased the relative abundance of the bacterial phyla Bacteroidetes and increased the abundance of Firmicutes as compared to SCD. The ratio between Firmicutes to Bacteroidetes was shifted towards control conditions upon atorvastatin treatment.

Conclusions
The results of this study suggest a regulatory impact of atorvastatin on the gut-microbial profile and, in turn, a crucial role of the gut-microbiome for the LDL-C lowering effect of atorvastatin independent of its regulation of hepatic cholesterol synthesis. Our findings provide novel insight into potential microbiota-related mechanisms causing interindividual variation in LDL-C lowering effects of statins.