the OATP1B1*15 haplotype. Separate studies have demonstrated that the OATP1B*15 haplotype has reduced transporting activity for atorvastatin (51).

Van de Steeg et al. (52) provides an excellent "big picture" summary of the consequences of the Val174Ala variant:

> In particular, the OATP1B1*15 variant (Asn130Asp and Val174Ala), with an average … frequency of 16–24% in Europe and America … is generally known to have a … **reduced transport activity** and has been associated with … increased plasma levels of certain OATP1B1 substrates … **decreased hepatic uptake** by OATP1B1*15 might result in decreased pharmacological response and give rise to unforeseen toxic side effects. Indeed, it has been demonstrated that patients carrying the OATP1B1*15 variant show … increased plasma levels, decreased pharmacological response, and even increased extrahepatic toxicity, for instance, after pravastatin, pitavastatin, or rosuvastatin treatment.

A number of drugs, such as cyclosporin A, can inhibit the transporting activity of OATP1B1. As a consequence, when patients are treated with statin and cyclosporin A, the plasma levels of the statin drug can increase to unexpectedly high levels (53). Increased levels of statins in the bloodstream, for example, as caused by impaired transport into hepatocytes, can result in statin-induced adverse events such as myopathy and rhabodomyolysis (skeletal muscle damage) (54,55).

i. Drug–Drug Interactions Distinguished From Adverse Events From Other Drugs That Do Not Involve Drug–Drug Interactions

Adverse events resulting from drug–drug interactions should be distinguished from adverse events from concurrent medications that result from mechanisms that do not involve drug–drug interactions. For example, the package label for televancin (56), which is an antibiotic that kills some types of bacteria, warns against diarrhea resulting from overgrowth of another type of gut bacterium, *Clostridium difficile*. It can readily be understood that this mechanism of action for producing diarrhea is independent from (and does not involve any drug–drug interaction) the mechanism of action for diarrhea, when taking drugs that prevent digestion of fats or carbohydrates (57). The following is another example of the same adverse events from two different drugs, but where there is no drug–drug interaction. According to the package label for the antibiotic, televancin, this drug may result in renal toxicity. The package label warns against taking concurrent medications that act on the kidneys,

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[52]van de Steeg E, Greupink R, Schreurs M, et al. Drug–drug interactions between rosuvastatin and oral antidiabetic drugs occurring at the level of OATP1B1. Drug Metab. Dispos. 2013;41:592–601.

[53]Karlgren M, et al. In vitro and In silico strategies to identify OAT1B1 inhibitors and predict clincal drug-drug interactions. Pharm. Res. 2012;29:411–26.

[54]Amundsen R, et al. Cyclosporin A, but not tacrolimus, shows relevant inhibition of organic anion-transporting protein 1B1-mediated transport of atorvastatin. Drug Metab. Dispos. 2010;38:1499–504.

[55]Ballantyne CM, et al. Risk for myopathy with statin therapy in high-risk patients. Arch. Intern. Med. 2003;163:553–64.

[56]Package insert for VIBATIV (telavancin) for injection, for intravenous use; December 2014 (37 pp.).

[57]Chassany O. Drug-induced diarrhoea. Drug Safety. 2000;22:53–72.