

metabolism and the consequent metabolism-dependent interconversion of active and inactive metabolites of atorvastatin. Conversion of the active acid form to the inactive lactone mainly requires an acylglucuronide intermediate (Prueksaritanont *et al.*, 2002). The latter is predominantly catalysed by UDP glucuronosyltransferase (UGT) 1A3 (Riedmaier *et al.*, 2010). Metabolism of the drug by cytochrome P450 (CYP) 3A4 results in the formation of the two active metabolites *ortho*-hydroxy and *para*-hydroxy atorvastatin (Jacobsen *et al.*, 2000). These two active metabolites are said to be responsible for the atorvastatin-related prolonged inhibition of HMGCR and the higher efficacy in lowering LDL cholesterol, as compared with other statins (Poli, 2007).

Disposition of a drug is also strongly influenced by transport processes. Hepatocellular uptake of atorvastatin, which is a substrate of the transporter SLCO1B1 (OATP1B1) (Kameyama *et al.*, 2005), is largely mediated by this membrane transport protein. For instance, atorvastatin pharmacokinetics is significantly altered by OATP1B1 inhibitors in humans (Lau *et al.*, 2007), as well as by SLCO1B1 genetic variants as shown by two independent studies (Pasanen *et al.*, 2007; Lee *et al.*, 2010). Moreover, atorvastatin is also a substrate of the efflux transporter ABCB1 (MDR1/P-glycoprotein) (Wu *et al.*, 2000; Hochman *et al.*, 2004), which influences pharmacokinetics of atorvastatin (Keskitalo *et al.*, 2008). Thus, multiple drug interactions because of the competitive inhibition of enzymes and/or transporters are conceivable and have been reported in the literature (see Lennernäs, 2003).

A series of large randomised endpoint trials (Lancet 1994) (*N Engl J Med* 1996) (*N Engl J Med* 1998;) (Athyros VG, Papageorgiou AA, Mercouris BR, 2002)(Serruys PW, de Feyter P, Macaya C, et al, 2002) (Shepherd J, Cobbe SM, Ford I, et al,1995) (Downs JR, Clearfield M, Weis S, et al., 1998) (Heart Protection Study Collaborative Group, 2002) (Prosper Study Group., 2002) (*JAMA* 2002)has established the benefits of statins for the prevention of major