



UNIVERSITY OF GOTHENBURG  
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**Abstract** - Master Thesis Project, the Pharmacy Programme

## **Associations between carboxylesterase 1 (CES1) polymorphism and cardiovascular outcomes**

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**Background** Carboxylesterase 1 (CES1) is an enzyme with broad substrate specificity, that is responsible for the activation of a number of ester prodrugs. Polymorphisms of the CES1 gene have been associated with alterations in the pharmacokinetics and drug response of some CES1 substrates. CES1 is also involved in cholesterol metabolism, with a possible role in atherosclerosis. The hypotheses in this master thesis were that there may be differences in survival between CES1 genotypes, through altered cholesterol homeostasis, decreased inactivation of clopidogrel and/or decreased activation of angiotensin converting enzyme (ACE) inhibitors.

**Methods** A large cohort of acute coronary syndrome patients enabled comparisons of outcomes between pharmacogenetic groups. Patients were genotyped for the CES1 mutation, p.Gly143Glu.

**Results** Genotype frequencies for p.Gly143Glu were 96.8% for the wild-type and 3.2% for the heterozygote, consistent with previous studies in Caucasians. The heterozygous p.Gly143Glu genotype in the overall cohort was significantly associated with better survival when adjusted for covariates ( $p=0.024$ ) but not when unadjusted ( $p=0.140$ ). In patients on ACE-inhibitor treatment a similar effect of the heterozygote on survival was noted (covariate-adjusted:  $p=0.020$ , unadjusted:  $p=0.371$ ). Clopidogrel was associated with a marked decrease in mortality ( $p=0.0001$ ), but there was no difference between the two genotype groups ( $p=0.230$ ).

**Conclusions** The heterozygous p.Gly143Glu genotype when adjusted for covariates, was associated with better survival in the overall cohort and in patients on ACE-inhibitor treatment. There was no effect in clopidogrel treated patients. These results suggest that CES1 polymorphism may affect survival, but not through altered prodrug activation.