Heart, Lung and Circulation (2019) **28,** e104–e105
1443-9506/04/$36.00
https://doi.org/10.1016/j.hlc.2018.10.017

Haptoglobin Genotype as a Prognostic Factor for Adverse Events in Coronary Artery Bypass Surgery in Diabetic Patients

To the Editor,

Type 2 diabetes mellitus (DM) is recognised as a risk of poor outcome of angioplasty and coronary artery bypass grafting (CABG). Haptoglobin (Hp) is a plasma haemoglobin-binding protein with three phenotypes: Hp1-1, Hp2-1, and Hp2-2. The Hp-1 protein is capable of rapidly removing free haemoglobin from circulation and thereby prevents the haemoglobin–iron-stimulated peroxidation of lipids, whereas the Hp 2-2 protein is a less efficient antioxidant. Numerous reports have demonstrated that an allelic polymorphism in the gene coding haptoglobin is a central determinant of susceptibility to microvascular and macrovascular complications in diabetic patients. Using a longitudinal population-based study design, Levy and colleagues [1] found a five-fold higher risk of cardiovascular disease (CVD) in patients with DM bearing the Hp2-2 phenotype versus those with the Hp-1-1 phenotype, and an intermediate risk was found in patients with Hp2-1. Several studies reported that, in diabetic individuals, the Hp genotype is a highly significant independent predictor of major adverse cardiovascular events in the first year after percutaneous transluminal coronary angioplasty (PTCA) and is associated with the risk of restenosis following PTCA and percutaneous coronary intervention (PCI) [2]. The increased prevalence of the Hp-2 allele in patients with more severe coronary artery disease may point to its possible causative role in the evolution of atherosclerosis. The Associations between Diabetes care and Haptoglobin genotype On outcomes (ADHOC) trial comprised 3,044 DM individuals, that underwent haptoglobin genotyping between 2 March 2005 and 26 September 2006; 124 patients required coronary artery bypass graft (CABG) surgery during the 8-year survey period (2005–2012) and formed the final cohort for the present study. Two hundred and eighty-five (285) (9.4%) had the Hp-1-1 phenotype, 1,248 (41.0%) Hp-2-1, and 1,511 (49.6%) Hp-2-2 (a similar distribution of patients had undergone CABG). Demographics as well as cardiac function were similar in the two cohorts e.g. the Hp-1-1 and the Hp-2 genotype group.

To determine the contribution of the Hp allele to CABG outcomes, we evaluated surrogate markers. Bypass time and cross-clamp time were longer than the median time (80 m and 53 m, respectively) for the Hp-2 group ($p = 0.04$, $p = 0.003$, respectively), this finding might be attributed to the microvascular complications associated with the Hp phenotype e.g. the quality of the coronary arteries and the associated difficulty of preforming the anastomosis might have caused the difference in bypass and cross-clamp times. Hospitalisation was longer than the median (5 days) for the Hp-2 group ($p = 0.037$), and the long-term survival was lower ($p = 0.025$), attesting on the general sickness of these patients, their DM in general and their Hp phenotype specifically (Figure 1).

Our results confirm and extend the generalisability of Roguin and others [3], wherein the Hp genotype was found to be associated with the incidence of stent restenosis.

They are also in line with earlier reports of shorter coronary graft survival times in patients with the Hp2-2 genotype [4].

The present study suggests that diabetic carriers of the Hp-2 allele who undergo CABG are more likely to have an increased operative related complexity than patients with the Hp-1 genotype. One can attribute the results of this study to the differential antioxidant capacity conferred on patients by these different phenotypes/genotypes. This assumption is supported by the I-CARE study [5], which demonstrated possible benefit from antioxidant treatment with vitamin E in these cases. The study findings provide a genetic basis for some of the variability seen in CABG outcome. As such, the Hp genotype may serve as a useful factor for identifying patients who will suffer from a more complicated operation and postoperative course or are at risk of early death. Confirmation of such an association will lay the ground for personalised preventative treatment based on Hp genotyping, in addition to documented risk factors.

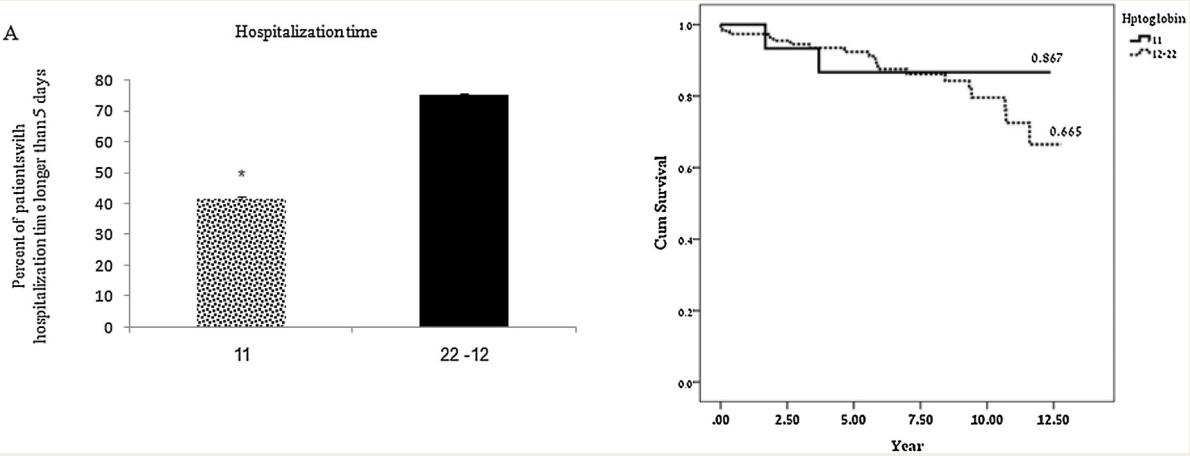

Figure 1 A. The percentage of patients caring the Hp-2 alleles that were hospitalised for more than 5 days was higher (5 days was the median hospitalisation time in the study group); p = 0.037. B. Survival curves drafted demonstrate a reduction in survival in the Hp-2 allele group; p = 0.025.

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Received 2 August 2018

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