Genetics and therapy of familial hypercholesterolemia

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CHAPTER 11

Summary

- Summary
- Conclusions
SUMMARY

Chapter 1 is the general introduction to this thesis and provides an overview of the history of FH, an explanation of intima-media thickness measurements and the methods and design of the ExPRESS study. In the first part of this thesis (Chapter 2 and 3) baseline characteristics and cardiovascular risk factors of the studied FH cohort are described. In the second part of this thesis (Chapter 4, 5 and 6) the treatment effects of simvastatin 80 mg on lipids and lipoproteins are described. In the third part of this thesis (Chapter 7, 8 and 9) the use of B-mode ultrasound as a non-invasive surrogate marker of CVD and the effect of statin therapy on the inhibition of the progression of atherosclerosis are described. In the last part (Chapter 10) we studied the effect of different LDL-receptor mutations on baseline lipids, presence of CVD and the effect of simvastatin therapy.

In Chapter 2 we evaluated the contribution of risk factors to the onset of cardiovascular disease (CVD) in FH. In 526 patients the prevalence of CVD was 37% with a mean age of onset of 46.8 years. In univariate analysis, age, presence of hypertension or diabetes, body mass index, triglycerides (TG) and low HDL-C were all significantly associated with CVD. Also in multivariate analysis, all these risk factors, except TG and diabetes, were significantly linked to CVD. Therefore, the extreme CVD risk in this large well-documented characterised sample of FH patients is not only conferred by elevated LDL-C but also by low HDL-C.

In Chapter 3 we examined in 507 FH patients whether low concentrations of bilirubin levels were associated with an increased risk for coronary artery disease. Median baseline bilirubin levels were significantly lower in male patients with CVD compared to those without. In particular, bilirubin was inversely related to the presence of CVD, both in univariate and multivariate analyses after adjustment for age, gender, presence of hypertension and high-density lipoprotein cholesterol levels. We hypothesise that high bilirubin levels might protect FH patients from CVD.

In Chapter 4 safety and efficacy data are given for 80 mg of simvastatin prescribed to 508 FH patients over a two-year period. At the time we initiated this study in 1997, 80 mg simvastatin was not yet approved by the national authorities. After 2 years of treatment total cholesterol levels were reduced by 39.2% to mean levels of 6.31 mmol/L (243 mg/dl) and LDL-C levels by 48.0% to mean levels of 4.29 mmol/L (165 mg/dl). TG levels were reduced by 26.1% to median levels of 1.20 mmol/L.
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(106 mg/dl). HDL-C levels were raised by 12.7% to mean levels of 1.35 mmol/L (52 mg/dl). All these changes from baseline were highly statistically significant. All changes in lipids were maintained throughout the study at different time points. Therefore, tachyphylaxis to simvastatin did not occur. Furthermore, simvastatin 80 mg was very well tolerated and safe.

In Chapter 5 we showed that LDL-C reduction was influenced by baseline LDL-C levels ranging from 51.1 to 45.5% in the top versus the bottom third of the LDL-C distribution. Unexpected in FH, elevated baseline TG levels were seen in 30% and low HDL-c levels in 15% of all patients. Also, simvastatin induced changes in these lipoproteins were dependent on baseline levels. Therefore, the greatest benefit from high-dose simvastatin treatment was obtained in FH patients with the worst lipoprotein profile.

In Chapter 6 we investigated whether baseline remnant-like particles (RLP-C) levels, which have been associated with the presence and progression of atherosclerotic disease, were elevated in FH. Indeed, we found that in 327 FH patients median RLP-C levels were severely elevated compared to controls (0.47 mmol/L vs. 0.20 mmol/L; p<0.0001). These elevated RLP-C levels could be the consequence of impaired function of the LDL-receptor in FH. After treatment, RLP-C levels were reduced by 49%. Therefore, baseline RLP-C levels are severely elevated in FH patients, are reduced by simvastatin, but do not return to normal levels. RLP-C levels in FH might contribute to an atherogenic lipoprotein profile and could identify patients who require additional treatment.

In Chapter 7 we assessed 153 FH patients and found an elevated mean combined baseline IMT of 1.07 ± 0.23 mm. After treatment with 80 mg simvastatin for 2 years, this IMT decreased by -0.081 mm (95% CI; -0.109 to -0.053; p<0.0001) with the largest reduction in the femoral artery. Strikingly, an actual decrease of combined IMT was seen in 69.8% of all patients. In conclusion, baseline IMT measurements were elevated in FH and were decreased by simvastatin treatment in the majority of the patients.

In Chapter 8 we investigated the association of homocysteine levels obtained in 1110 FH patients and IMT measurements. In FH patients with cardiovascular disease (37%) median plasma homocysteine levels were increased compared to disease-free patients. In addition, the MTHFR TT-genotype, a genetic cause of hyperhomocysteinemia, showed significantly higher median levels of homocysteine than the CC-genotype. Nevertheless, no relationship became evident between MTHFR-genotype, cardiovascular disease or IMT, neither between homocysteine and
cardiovascular disease are indeed associated in FH, but our data suggest hyperhomocysteinemia to be a consequence rather than a cause of this disease process. In Chapter 9 the effect of simvastatin treatment on coagulation and fibrinolysis parameters were studies in relation to IMT. Simvastatin therapy produced small but significant changes in a number of hemostatic parameters. An increase was observed for fibrinogen, coagulation factor VIII, von Willebrand Factor, D-dimer and plasminogen activator inhibitor type 1 (PAI-1), whereas prothrombin fragment 1+2 and prothrombin were decreased. Nevertheless, all these alterations in coagulation and fibrinolysis parameters were not related with IMT changes over a 2-year treatment period.

In Chapter 10 we studied in 344 FH patients the effect of 71 different LDL-receptor mutations on baseline lipids and the effect of simvastatin therapy. Baseline LDL-C levels were higher in mutations with a receptor-activity ≤ 5% compared to a receptor-activity >5%. Most importantly, no difference was found in the 2 groups with regards to maximal LDL-C reduction with simvastatin treatment.

**CONCLUDING REMARKS**

1. Besides traditional risk factors for CVD, such as age, body mass index, presence of hypertension or diabetes, two other parameters, namely low levels of HDL-C and bilirubin, turned out to influence presence of CVD in FH.
2. Long term treatment with simvastatin 80 mg is efficacious and safe in FH patients.
3. Unexpectedly, at baseline, a third of FH patients had high TG levels and 15 % had low HDL-C levels. Furthermore, treatment with simvastatin was dependent on baseline lipid levels. Therefore, FH patients with the worst lipoprotein profile showed the greatest benefit from high-dose simvastatin treatment.
4. Remnant like particles are elevated in FH patients and reduced, but not to normal levels, by simvastatin therapy.
5. FH patients exhibit marked intima-media thickening and simvastatin results in regression of IMT in the majority of FH patients.
6. Homocysteine and cardiovascular disease are associated in FH, but hyperhomocysteinemia seems to be a consequence rather than a cause of this disease process.
7. In FH patients, both coagulation and fibrinolysis parameters were significantly affected by simvastatin 80 mg. However, these changes were not associated with changes in IMT.

8. Mutations with a receptor-activity ≤5% exhibit higher LDL-C levels compared to mutations with a receptor-activity >5% however, do not differ in response to therapy with simvastatin 80 mg.