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The lipoprotein lipase gene serine 447 stop variant influences hypertension-induced left ventricular hypertrophy and risk of coronary heart disease

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Short title: *LPL* S447X affects hypertension-induced LVH and CHD risk

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Abstract

Background Left ventricular hypertrophy (LVH) is an independent risk factor for coronary heart disease (CHD). During LVH, the preferred cardiac energy substrate switches from fatty acids (FA) to glucose. Lipoprotein lipase (LPL) is the key enzyme in triglyceride hydrolysis and supplies FA to the heart. To investigate whether substrate utilisation influences cardiac growth and CHD risk, we examined the association between the functional *LPL* S447X (rs328) variant and hypertension-induced LV growth and CHD risk. LPL-447 has been shown to be more hydrolytically efficient and would therefore release more free FAs than LPL-S477.

Methods and results: In a cohort of 190 hypertensive subjects, *LPL* X447 was associated with greater LV mass index (SS 85.2±1.7, SX+XX 91.1±3.4, p=0.01), but no such association was seen in normotensive controls (n=60). X447 allele frequency was higher in hypertensives with LVH than those without LVH (LVH 0.14, 95%CI 0.08-0.19; non-LVH 0.07, 95%CI 0.05-0.10; Odds Ratio 2.52, 95%CI 1.17-5.40 p=0.02). The association of *LPL* S447X with CHD risk was then examined in a prospective study of healthy middle-aged UK men (n=2716). In the normotensive individuals, compared to S447 homozygotes, X447 carriers were protected from CHD risk (Hazard Ratio [HR] 0.48, 95%CI 0.23-1.00, p=0.05), whilst in the hypertensives, X447 carriers had increased risk (HR: SS 1.54, 95%CI 1.13-2.09, p=0.006; X447+ 2.30, 95%CI 1.53-3.45, p<0.0001) and showed significant interaction with hypertension in CHD risk determination (p=0.007).

Conclusions Hypertensive *LPL* X447 carriers have increased risk of LVH and CHD, suggesting that altered FA delivery constitutes a mechanism through which LVH and CHD are associated in hypertensive subjects.

Key Words fatty acids, genetics, hypertrophy, hypertension, coronary heart disease, lipoprotein lipase, *LPL*S447X

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Introduction:

Left ventricular hypertrophy (LVH) is an independent risk factor for cardiovascular disease (CVD) [1-3]. The association between LVH and CVD remains poorly understood, but hypertension is a common stimulus for LVH [4] and is itself a powerful risk factor for CVD [5] and heart failure[6].

In pathological situations such as ischemia and hypertrophy, the heart switches substrate utilisation from predominantly fatty acid (FA) oxidation (FAO)[7] to glucose and lactate catabolism [8,9]. Substrate switching is thought to be an oxygen-sparing mechanism, as glucose utilisation requires less oxygen per mole of ATP generated than FAO. A number of lines of evidence suggest a direct role for FA metabolism in the pathogenesis and progression of LVH. Firstly, dyslipidaemia and an unfavourable FA profile predict LVH over a 20 year period [10]. Furthermore, cardiac FA metabolism is an independent predictor of LV mass in hypertensive heart disease [11] whilst FAO inhibitors prevent LV dilatation in the pressure-overloaded rat heart [12], and show promising results in human studies on the treatment of coronary heart disease (CHD) and heart failure [13].

Lipoprotein lipase (LPL) is the key enzyme in plasma triglyceride hydrolysis, liberating FA for energy generation in the heart. LPL is highly expressed in adult heart [14] and is down regulated in the hypertrophied heart of the SHR rat [15,16] and in endothelin-treated neonatal rat cardiomyocytes [15]. Variation in the *LPL* gene is associated with altered plasma triglyceride levels, and variants associated with lower LPL activity (D9N, rs1801177, and N291S, rs268) are associated with increased risk of CHD [17,18]. The serine 447 stop (S447X, rs328) variant deletes two amino acids from the carboxy-terminal of *LPL* and LPL-X447 is more active *in vitro* [19]. The X447 allele is associated with increased LPL activity, lower plasma triglycerides, higher HDL and reduced risk of CHD [17,18,20,21]

We recently observed association between peroxisome proliferator-activated receptor alpha (PPARα), a key regulator of cardiac fatty acid catabolism [22], and exercise- and hypertension-induced LVH [23], suggesting that cardiac FA utilisation directly influences the cardiac growth response. To investigate further the role of FA utilisation in LV growth, we examined association between the *LPL* S447X variant and hypertension-induced LVH [24], and in hypertension-associated risk of CHD in 2716 healthy UK middle-aged men participating in the prospective Second Northwick Park Heart Study (NPHSII) [25].

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Methods

Study subjects

Leeds LVH Study: Sixty Caucasian normotensive volunteers (30 male, 30 female) were recruited to determine the normal range of LV mass. Two hundred and five Caucasian patients with essential hypertension, defined either as a history of essential hypertension (85%) or newly diagnosed with 2 sitting readings of systolic blood pressure ≥ 160 mm Hg and/or diastolic blood pressure ≥ 100 mm Hg, were recruited from cardiology outpatient clinics. Genotype data was available on 57 normotensive and 190 hypertensive subjects. Patients with a history of valvular heart disease, previous myocardial infarction (MI) and arrhythmias were excluded. Cardiac MRI was performed to accurately determine LV mass as previously reported.[24] Written informed consent was obtained from all subjects and the local ethics committee approved the study.

The Second Northwick Park Heart Study (NPHSII). NPHSII is a prospective study of unrelated healthy middle-aged UK men (mean age 56.1±3.5 years) recruited from nine UK general practices and followed prospectively for a median of 10.8 years (range 7 days to 13.2 years) [25]. Exclusion criteria were a history of MI, cerebrovascular disease, life-threatening malignancy or regular medication with aspirin or anticoagulants. CHD was defined as sudden cardiac death, symptomatic or silent (ECG) MI or coronary revascularisation, and time to first event was recorded. In the 2716 eligible Caucasian subjects for whom LPL S447X genotype was available, there were 219 events, comprising 156 (71%) acute MI, 42 (19%) coronary surgery and 21 (10%) silent MI. Plasma lipid and lipoprotein levels were determined at baseline. At entry, systolic and diastolic blood pressure (SBP and DBP) were recorded twice with a random zero mercury sphygmomanometer after five minutes seated. Written informed consent was obtained from all subjects and approval was given by the institutional ethics committees. *LPL* gene S447X (rs328) genotype was determined by PCR-RFLP analysis using HinfI digestion (New England Biolabs) [26].

Statistical analysis

The maximum number of genotypes available for each parameter was analysed. Hardy-Weinberg equilibrium was examined using chi-squared test. In the Leeds LVH study, the X447 homozygotes were combined with X447 carriers for all analyses. SPSS Version 12 (SPSS Inc., Chicago, Illinois) was used for statistical analysis. The effect of S447X genotype

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on measures of blood pressure and LV mass were examined using univariate analysis of variance (ANOVA) and linear regression. Genotype, and covariates age, BMI, current smoking, gender, and in analysis of LV mass, number of anti-hypertensive medications and SBP were added. Factors and covariates were all included in the initial model and removed in a stepwise manner to generate the most parsimonious model. Binary logistic regression analysis was used to examine the effect of genotype on the presence of LVH.

In NPHSII, analysis was performed using 'Intercooled' STATA (version 8.2 STATA Corporation, Texas). Results are presented as mean ± standard deviation (SD). Plasma concentrations of triglyceride, apoB and HDL were not normally distributed and were log transformed. Comparisons of baseline characteristics were made using ANOVA or chi-squared tests. Adjustments were made by the inclusion of covariates in the models. The effects of hypertension and genotype on lipids were assessed by two-way analysis of variance. Survival analysis was carried out using Cox proportional hazards model. Results are presented as hazard ratios (HR) with 95% confidence intervals (CI). A p- value of 0.05 was taken as statistically significant. Estimated probabilities were obtained from logistic regression models and plotted to illustrate the increase in risk with blood pressure.

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Results

LPL S447X variant and hypertension-induced cardiac growth

The characteristics of the Leeds LVH study are shown in Table 1. *LPL* S447X genotype was available in 57 normotensive and 190 hypertensive subjects. Genotype distributions were in Hardy-Weinberg equilibrium in the entire study and in normotensive and hypertensive subgroups separately. The X447 allele frequency was no different in the normotensive subjects compared to the hypertensives [0.09 (95% CI 0.04-0.140) vs.0.09 (0.06-0.12), respectively.

The association between S447X genotype and left ventricular mass indexed to body surface area (LVMI) was examined. In the hypertensive subjects, there was no heterogeneity of effect between men and women (data not shown) and in the group as a whole X447 carriers had significantly higher LVMI (91.1±3.4) than S447 homozygotes (85.2±1.7, p=0.013) after adjustment for age, gender, SBP and number of antihypertensive medications, all independent predictors of LVMI (Table 2). The β-coefficient for the X447 allele was +7.2±3.2 g/m^2. S447X genotype did not influence LVMI in normotensive subjects (SS 69.5±1.7, SX+XX 67.8±3.0 g/m^2, p=0.67).

In the hypertensive group, 74 subjects (39.0%) had LVH, defined as greater than the mean of normotensive individuals plus 2 SD (males 77.8±9.1 g/m^2, females 61.5±7.5g/m^2). X447 carriers had significantly greater prevalence of LVH than S447 homozygotes (57.5% vs. 35%, respectively, p=0.013) with an odds ratio for LVH 2.52 (95% CI 1.17-5.40, p=0.02) compared to S447 homozygotes. This effect was observed both in males (O.R. 2.95, 95% CI 1.09-7.96, p=0.03) and in females, although this did not reach statistical significance (O.R. 2.05, 95% CI 0.56-7.43, p=0.26).

LPL S447X variant and hypertension-associated risk of ischemic heart disease in NPHSII

The association between *LPL* S447X genotype and hypertension-induced LVH indicated that *LPL* S447X may also modulate risk of CHD in hypertensive subjects. This hypothesis was investigated in the Second Northwick Park Heart Study. The baseline characteristics of participants are shown in Table 3. The X447 allele frequency was 0.103 (95% CI 0.094-0.111) and genotype distribution was in Hardy Weinberg equilibrium in the whole study and in normotensive and hypertensive subgroups. X447 allele frequency did not

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differ between the Leeds LVH study and NPHSII (p=0.42), nor between normotensive and hypertensive individuals in NPHSII (normotensive 0.11, 95% CI 0.09-0.12; hypertensive 0.10, 95% CI 0.09-0.11, p=0.45). Association was examined between *LPL* S447X and plasma lipid and apolipoprotein levels (Table 4). The X447 carriers had 6.6% lower plasma triglycerides (P=0.008), 5% higher HDL cholesterol (p=0.01) and 3% higher apoAI (p=0.005) than S447 homozygotes.

The impact of the *LPL* S447X variant on prospective CHD risk was examined. Overall, S447X genotype did not influence CHD risk, S447X allele frequencies being the same in CHD cases and healthy control subjects (Table 3) This was reflected in survival analysis where X447 carriers had a hazard ratio (HR) of 1.06 (95% CI 0.76-1.48, p=0.72).

The relationship between CHD risk and SBP as a continuous variable was examined. There was a linear relationship between increasing SBP and increasing CHD risk (Figure 1A). SBP was an independent risk factor for CHD in NPHSII (p=0.0003) and the risk associated with a 1 SD (19.2 mm Hg) increase in SBP was 1.35 (95%CI 1.19-1.53, p<0.0001). The influence of *LPL* S447X genotype on the relationship between CHD risk and SBP was then considered (Figure 1B). In normotensive X447 carriers, increasing SBP had a greater effect on CHD risk in carriers than in S447 homozygotes. CHD risk was examined in subjects stratified by hypertensive status (SBP≥140 or DBP≥90 mm Hg or antihypertensive medication), which divides the study into approximately equally sized groups (normotensive n=1282, hypertensive n=1432). Unadjusted survival analysis of the interaction between S447X genotype and hypertension on risk of CHD over time is presented graphically as a Kaplan-Meier survival plot (Figure 2). There was significant interaction between S447X genotype and hypertension on CHD risk (unadjusted p=0.007). With normotensive S447 homozygotes as the reference group, after adjustment for traditional risk factors of age, practice, BMI, cholesterol, triglycerides and smoking status, normotensive X447 carriers had a reduced risk of CHD (HR 0.46 95% CI 0.24-0.94, p=0.02). However this effect was reversed in the hypertensive subjects. Compared to normotensive subjects, the hypertensive S447 homozygotes had increased risk of CHD (HR 1.22, 95% CI 0.89-1.68, p=0.21), but this was not statistically significant, while hypertensive X447 carriers had significant increase in CHD risk (HR 1.83, 95% CI 1.20-2.77, P=0.005) (Figure 3), with significant interaction between S447X genotype

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and hypertension on CHD risk (p=0.007). In X447 carriers, the presence of hypertension was associated with an HR of 4.78 (95% CI 2.22-10.28, p=0.00002).

To study whether the impact of *LPL* genotype on CHD risk was mediated through effects on plasma triglyceride concentrations, we examined the association of S447X with plasma lipid levels in normotensive and hypertensive subjects (Table 5). Overall, plasma triglyceride levels were significantly higher in hypertensive than in normotensive subjects (1.95 mmol/L $\pm$ 1.04 and 1.64 mmol/L $\pm$ 0.84, respectively, p<0.0001). A borderline significant interaction was observed between S447X genotype and hypertension on plasma triglycerides, with the X447 associated with lower triglycerides in hypertensive subjects (SS: 1.99 mmol/L $\pm$ 1.08; X447+ 1.78 mmol/L $\pm$ 0.88, p=0.002), but not in normotensive subjects (SS: 1.65 mmol/L $\pm$ 0.84; X+ 1.63 mmol/L $\pm$ 0.82, p=0.73, P for interaction 0.05) (Table 5). When the CHD risk analysis was then adjusted for the effect of plasma triglycerides, the X447 allele was protective in normotensive subjects (H.R. 0.48, 95% CI 0.23-1.01, p=0.05). However, in the hypertensive subjects X447 carriers showed a marked increase in CHD risk (H.R. 2.22, 95% CI 1.48-3.33, p<0.001), whilst hypertensive S447 allele homozygotes had a borderline increased risk of CHD (H.R. 1.38, 95% CI 1.01-1.88, p=0.04) and the interaction remained significant (p=0.004)

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Discussion

These results demonstrate that in hypertensive subjects the *LPL* X447 allele is associated both with greater cardiac growth and with higher risk of CHD, while in normotensive subjects, the X447 allele did not influence cardiac mass and was *protective* against risk of CHD. LVH is an independent risk factor for cardiovascular morbidity and mortality [27], and is associated with increased prevalence of CHD [4], stroke [28], congestive heart failure [29]and sudden cardiac death [3]. Hypertension is a major risk factor for these disorders, and our observations provide genetic evidence that cardiac energy metabolism may constitute a link between hypertension, LVH and cardiovascular disease.

There is increasing evidence that cardiac substrate utilisation directly influences cardiac function and structure. We previously demonstrated that genetic variation in PPARα, a master regulator of cardiac FAO, influenced hypertension-induced cardiac growth [23]. Mutations in FAO genes or mitochondrial DNA cause hypertrophic cardiomyopathy and/or heart failure[30]. Myocardial FAO is an independent predictor of LV mass in hypertensive heart disease [11]. Conversely, in type 2 diabetic subjects, whose hearts are almost totally reliant on FAO [31], LV mass is greater [32] and LVH is more prevalent [33] than in non-diabetic subjects. Partial FAO inhibitors such as ranolazine, trimetazidine and perhexiline have beneficial effects on angina and heart failure [34]. These data indicate that the appropriate regulation of substrate utilisation is central to the maintenance of appropriate cardiac mass, and dysregulation is detrimental to cardiac structure and function. The association between the X447 allele and increased LV mass index and CHD risk in hypertensives supports this hypothesis. Furthermore these data indicate that the detrimental effect of the X447 allele in hypertensive subjects is not mediated through systemic effects on plasma lipids. Higher plasma triglycerides are associated with increased LV mass [10] and are an independent risk factor for CHD[35]. The X447 allele is consistently associated with lower plasma triglycerides [17,18], and our data demonstrates that hypertensive X447 carriers have significantly lower triglycerides than hypertensive S447 homozygotes. The X447 allele has been inconsistently associated with moderately lower CHD risk in some, but not all, studies, with an odds ratio of 0.8 in two meta-analyses [17,18]. Our observation that the X447 allele is associated with 50% *decreased* risk in normotensive subjects, but 2.3-fold *increased* risk in hypertensive subjects, may explain some of the previously observed inconsistencies, as

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interaction with hypertension was not examined previously. Thus our current studies suggest a direct cardiac effect in which increased cardiac FA availability in the overloaded hypertensive heart of X447 carriers may be detrimental to cardiac function, thus further driving cardiac growth and increasing cardiovascular risk.

Templeton et al resequenced the *LPL* gene and identified 69 SNPs defining 88 haplotypes. They concluded that recombinational and mutational hotspots played significant roles in determining the haplotype variation at the *LPL* locus, and while the central genomic region had common SNPs the 5' region showed population specific variability [36], which makes tSNP analysis difficult. Three functional *LPL* SNPs have been well studied and association studies have identified a role for these *LPL* variants in the determination of IHD risk. D9N and N291S have been associated with increased IHD risk[17,18], with the N9 allele showing a strong interaction with smoking status.[37] The functional basis for these associations has been identified; while the S291N variant leads to loss of LPL dimer stability and therefore reduced hydrolytic function (since the LPL monomer is inactive) [38], the substitution of Asparagine for Aspartic acid (D9N) leads to an altered charge on the protein, which enhances binding to heparin sulphate proteoglycans and increased bridging function . [39] These two SNPs have rare allele frequencies ranging from 0.03-0.06 and show no linkage disequilibrium [40]. The S447S variant has increased enzyme activity and as such has been used to rescue the lethality in *Lpl* knockout mice, and does so more effectively than wildtype *LPL* [41]. The rare allele frequency of S447X is close to 0.20 and although it shows strong negative LD with S291N and D9N the latter two are rare and are unlikely to play a major part in this analysis.

In NPHS2, X447 was associated with *lower* triglycerides in hypertensive, but not normotensive subjects. Thus the effect of *LPL* S447X genotype on plasma triglycerides could not explain the increased risk in hypertensive X447 allele carriers, as this subgroup has the highest CHD risk but significantly lower plasma triglycerides than hypertensive S447 homozygotes. This was confirmed when CHD risk adjusted for plasma triglycerides produced the same pattern of results. At recruitment no subjects were taking ACE inhibitors, Angiotensin 2 Receptor blockers or statins and although a proportion of those who developed CHD over follow-up may have been prescribed such medications this is unlikely to have

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confounded the genetic effect on risk observed here, but would rather have the effect of diluting it.

The mechanisms underlying the increased risk of CHD in hypertensive X447 allele carriers remain unclear. Transgenic experiments indicate that global LPL overexpression is atheroprotective [42], whilst macrophage LPL expression is proatherogenic [43], smooth muscle cell overexpression causes vascular dysfunction [44], skeletal and cardiac muscle overexpression causes severe myopathy, weight loss and premature death[45], whilst cardiomyocyte membrane-bound LPL overexpression causes dilated cardiomyopathy [46]. However, such ectopic or overexpression experiments may be non-physiological with limited relevance to human disease.

The limitation of this study is the small number of NT individuals in the Leeds study, and as with the genotype effect in the HT group, these data need to be confirmed in a larger study. However as a hypothesis generating study it does raise some interesting questions about the role of LPL in the heart. These results support a role for the *LPL* X447-associated increase in cardiac growth and risk of LVH in response to hypertension. Since the truncation of LPL by two amino acids (LPL-X447) leads to increased hydrolytic efficiency [47], this would generate increased cardiac FA availability which the data suggest is pro-hypertrophic. This suggests that substrate switching in LVH and ischemia is indeed a beneficial adaptive response. Furthermore, hypertensive X447 carriers had an increased prospective risk of CHD, promoting the possibility that the heart may be more susceptible to ischemia in situations of increased FA supply. These data provide genetic evidence for a role of substrate utilisation in cardiac structure, function and risk. Human substrate utilisation studies are needed to clarify the mechanisms underlying these effects.

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Figure Legends

Figure 1. The relationship between cardiovascular risk and SBP in NPHSII in A) 2716 subjects with genotype data (95% CI are shown as dotted lines); B) subjects stratified by *LPL* S447X genotype. S447 homozygotes are represented by the filled line, X447 allele carriers (SX+XX) are represented by the broken line.

Figure 2. Kaplan-Meier survival curves of CHD events by *LPL* S447X genotype in normotensive (NT) and hypertensive (HT) subjects.

Figure 3. CHD risk in NPHSII by *LPL* S447X genotype. Adjusted for age, practice, BMI, cholesterol triglyceride and smoking. Results are presented as hazard ratios with 95% CI. Numbers in parentheses are number of CHD events/subjects in each group.

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Table 1. Characteristics of the Leeds LVH study

	Normotensives (n=57)	Hypertensives (n=190)	p-value
Age, years	44.2±1.4	55.2±0.8	<0.001
Gender, % male	49.1	63.2	0.06
BMI, kg/m^2	26.3±0.5	29.9±0.4	<0.001
Sitting SBP, mm Hg	122.9±1.7	159.2±1.8	<0.001
LVMI, g/m^2	69.2±1.5	86.3±1.5	<0.001
S447X allele distribution (SS/SX/XX)	47/10/0	157/31/2	0.73
S447X allele frequency (95% CI)	0.088 (0.036-0.140)	0.092 (0.063-0.121)	0.89

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Table 2: Effect of *LPL* S447X variant on systolic BP and LVMI in hypertensive subjects in the LEEDS LVH study

	Ser/Ser n=157	Ser/X+X/X n=33	p- value	Adjusted p- value
SBP, mm Hg	159.6±2.1	157.6±3.2	0.68	-
DBP, mmHg	94.2±1.3	89.6±2.3	0.12	0.12
LVMI, g/m^2	85.2±1.7	91.1±3.4	0.14	0.014
LVH, %	35.0%	57.5%	0.018	0.012

Means ± SEM. P values adjusted for BMI, age, gender, SBP and number of anti-hypertensive medications

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Table 3: Baseline characteristics of the Second Northwick Park Heart Study by control or IHD case status

	Controls n=2497	IHD cases n=219	p-value
Age, years	56.0 (3.4)	56.6 (3.6)	0.009
Systolic blood pressure, mmHg	137.9 (19.1)	143.7 (19.9)	<0.0001
Diastolic blood pressure, mmHg	84.3 (11.2)	87.8 (11.6)	<0.0001
Current smoking, %	27.5%	36.1%	0.007
BMI, kg/m^2	26.4 (3.5)	27.1 (3.5)	0.004
Cholesterol, mmol/	5.71 (1.01)	6.04 (1.01)	<0.0001
Triglyceride, mmol/l	1.77 (1.23-2.53)	2.10 (1.43-2.98)	<0.0001
apoB, mg/L	0.86 (0.72-1.01)	0.92 (0.78-1.10)	0.0008
apoAI, mg/L	1.64 (0.32)	1.57 (0.27)	0.008
Fibrinogen, g/l	2.70 (2.38-3.02)	2.83 (2.47-3.19)	0.0005
LPL S447X variant (SS/SX/XX)	2014/456/27	175/41/3	0.91
X447 allele frequency (95%CI)	0.102 (0.094-0.111)	0.107 (0.078-0.136)	0.73

Mean (SD), except triglyceride, apoB and fibrinogen where geometric means and interquartile ranges are provided..

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Table 4: Plasma lipid, apolipoprotein and blood pressure measures in NPHSII by *LPL* S447X genotype

	Ser/Ser (n=2189)	Ser/X+X/X (n=527)	p-value	Adjusted p-value*
Triglyceride, mmol/L	1.82 (1.26-2.61)	1.70 (1.20-2.36)	0.008	<0.001
Cholesterol, mmol/L	5.72 (1.01)	5.79 (1.01)	0.16	0.06
HDL-cholesterol, mmol/L	0.79 (0.65-0.97)	0.83 (0.69-1.02)	0.01	0.009
apoAI, mg/L	1.62 (0.32)	1.67 (0.34)	0.005	0.04
apoB, mg/L	0.86 (0.73-1.02)	0.86 (0.71-1.01)	0.73	0.73
BMI, kg/m^2	26.4 (3.5)	26.6 (3.5)	0.38	0.09
SBP, mm Hg	138.4 (19.2)	138.4 (19.0)	0.97	0.99
DBP, mm Hg	84.6 (11.4)	84.6 (10.8)	0.99	0.88
Presence of hypertension, %	53.1%	51.3%	0.46	

Mean (SD), except triglyceride, apoB and HDL where geometric means are presented.

*P value adjusted for age, practice, BMI, smoking. Triglyceride and apolipoprotein measures adjusted additionally for cholesterol; blood pressure adjusted additionally for triglyceride.

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Table 5. Plasma lipid and apolipoprotein levels in normotensive and hypertensive NPHSII subjects.

	Normotensive subjects		Hypertensive subjects				
	Ser/Ser (n=1026)	**Ser/X+X/X (n=256)**	**Ser/Ser (n=1162)**	**Ser/X+X/X (n=270)**	**p-value genotype**	**p-value hypertension**	**p-value interaction**
Triglyceride, mmol/L	1.65 (1.17-2.26)	1.63 (1.11-2.23)	1.99 (1.35-2.86)	1.78 (1.26-2.50)	0.01	<0.0001	0.05
Cholesterol, mmol/L	5.61 (0.98)	5.70 (0.98)	5.81 (1.03)	5.88 (1.04)	0.13	<0.0001	0.84
HDL-cholesterol, mmol/L	0.81 (0.66-0.99)	0.86 (0.71-1.07)	0.78 (0.63-0.96)	0.80 (0.68-0.99)	0.02	<0.0001	0.48
apoAI, mg/L	1.63 (0.33)	1.63 (0.34)	1.62 (0.31)	1.66 (0.33)	0.005	0.50	0.50
apoB, mg/L	0.86 (0.72-1.02)	0.85 (0.70-1.00)	0.87 (0.73-1.01)	0.87 (0.73-1.04)	0.73	0.34	0.52

Mean (SD), except triglyceride, HDL-cholesterol and apoB where geometric means are provided.

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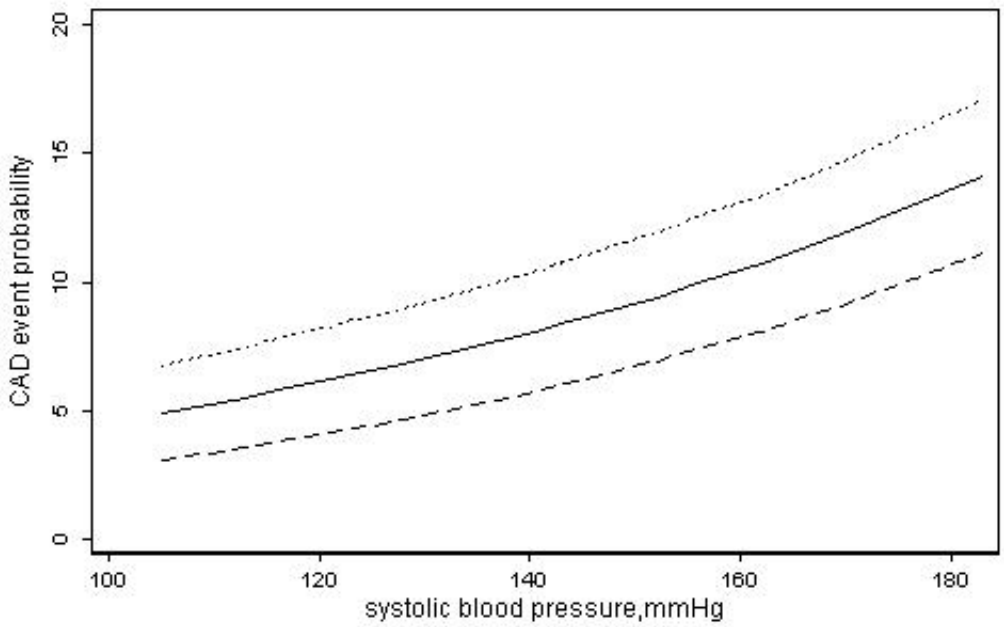
Figure 1

a)



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b)

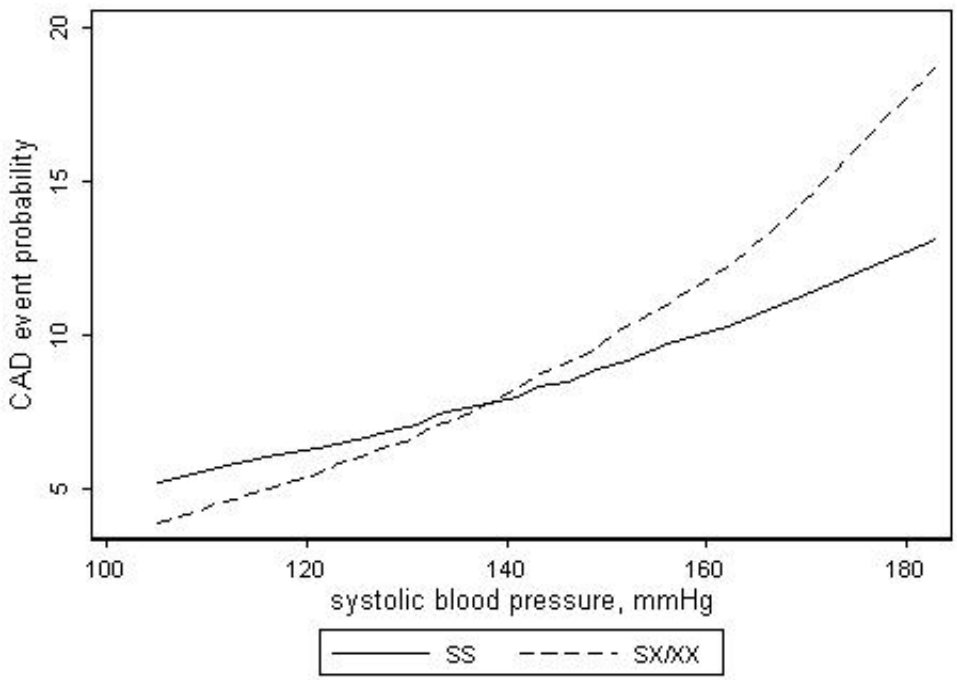

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Figure 2

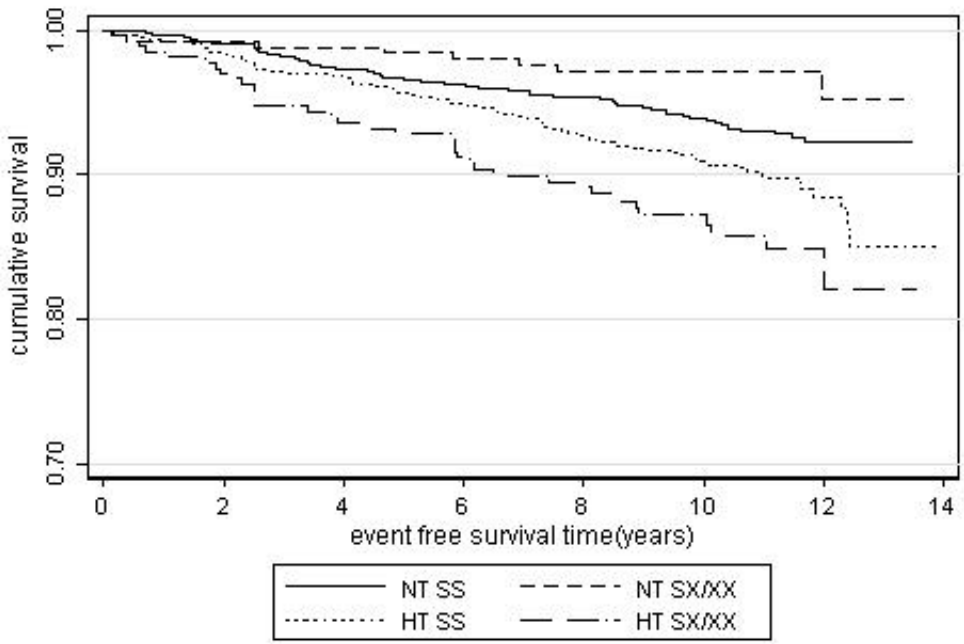

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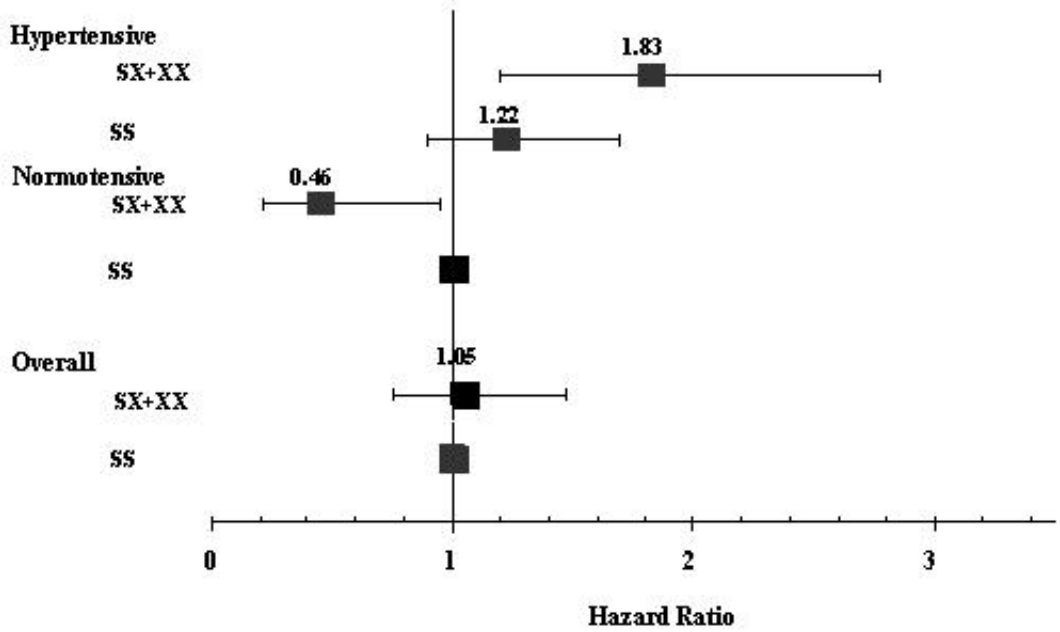
Figure 3



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