Table 1: Clinical characteristics of the Go-DARTS cohort

No of individuals	1810 (54% male)
Age at recruitment (years)	63.1 (9.6)
Age at diagnosis	54.9 (9.0)
Body Mass Index (kg/m^2)	30.5 (5.4)
Insulin treatment	839 (44.1%)
Smoking History	958 (50.4%)
Prevalent cerebrovascular disease	67 (3.5%)
Prevalent angina	178 (9.4%)
Previous myocardial infarction	323 (17.0%)

Data shown are mean (SD) for continuous variables and n (%) for categorical variables.

activated transcription factors. Ligands for PPARα include polyunsaturated fatty acids and the fibrate class of lipid-lowering drugs [2]. It is expressed at high levels in several cell types involved in the atherosclerotic process [3], and its activation has beneficial effects on plasma lipids, endothelial function and markers of inflammation [4]. Thus, the *PPARA* gene is a strong candidate for a genetic determinant of CVD risk in people with type 2 diabetes [5].

The *PPARA* gene has been screened for common variation [6-8]. The most studied variant is the leucine 162 valine (L162V) polymorphism, present at allele frequencies between 5 and 10%, and situated in the DNA binding domain. Functional studies have demonstrated that the V162 allele is more active *in vitro* [7,9], and the V162 allele has been associated with altered plasma lipid levels [6,8,10], delayed progression of angiographically determined CV disease in the Lopid Coronary Angiography Trial (LOCAT), and reduced risk of ischemic heart disease in the Second Northwick Park Heart Study (NPHS2) [11]. A second, more common, G→C variant situated in intron 7 (G2528C) is in partial allelic association with the L162V variant and shows opposing effects on cardiovascular risk and cardiac growth [9,11]. Recently it has been demonstrated that haplotypes of these variants in association with a further A→C variant in intron 1 influence age of onset of type 2 and time to requiring insulin [12].

PPARα activators improve the dyslipidemia associated with type 2 diabetes and may be particularly beneficial in lowering risk of CVD in subjects with type 2 diabetes or metabolic syndrome [13]. We therefore investigated the association between *PPARA* gene variation with risk of CVD and diabetes related traits in Caucasian subjects with type 2 diabetes participating in the prospective population-based Genetics of Diabetes Audit and Research in Tayside Scotland (Go-DARTS) study [14-16].

Results

The clinical characteristics of the genotyped cohort are shown in table 1. The allele frequencies of both polymorphisms were consistent with those previously published for European non-diabetic populations (table 2). The two polymorphisms were both in Hardy-Weinberg equilibrium and were in significant linkage disequilibrium D' = 0.204 p =< 0.00001. Estimated haplotype frequencies indicated very similar values with those previously published (table 3). There was little evidence that the genotypes either singly, or when included in the model together, were associated with blood pressure or lipid measurements (table 4). V162 was associated with a generally more cardioprotective profile with V/V homozygotes having lower systolic and diastolic blood pressure, lower LDL cholesterol and higher HDL cholesterol than L/L homozygotes, although none of these differences were significant. Conversely C2528 homozygotes had a small but significantly higher total cholesterol and calculated LDL cholesterol compared to G/G homozygotes. We also

Table 2: *PPARA* genotype distribution and allele frequencies in the Go-DARTS cohort. The corresponding allele frequencies from the Second Northwick Park Heart Study (NPHS2)[11] is shown for comparison.

		n			n
L162V	L/L	1573	**G2528C**	GG	1216
	L/V	224		GC	529
	V/V	13		CC	64
		1810			1809
Go-DARTS allele freq.		0.069 (0.061–0.077)			0.182 (0.169–0.194)
NPHS allele freq.		0.063			0.174