**Table 5: Influence of genotype and inferred haplotypes on age diagnosed with type 2 diabetes.**

| | Age diagnosed | | |
|---|---|---|---|
| | Beta | 95% CI | p |
| **V162*** | 2.6 | 0.2–5.1 | 0.034 |
| **C2528†** | -1.1 | -2.0–0.2 | 0.022 |
| **Haplotype** | | | |
| **L162-G2582** | Ref | | |
| **L162-C2528** | -0.40 | -1.25 – 0.45 | 0.36 |
| **V162-G2528** | 3.89 | 1.26 – 6.51 | 0.004 |
| **V162-C2528** | -0.28 | -1.65 – 1.10 | 0.69 |

*Co-dominant model
† Dominant model
Both variants included in the model

associated with the C2528 was not linked to raised cholesterol levels. When a combined endpoint of death from all cause, and non-fatal myocardial infarction was considered in the same model it was found that the V162 continued to demonstrate a reduced risk of an event although the association was attenuated (HR 0.52, 95%CI 0.28–0.98, p = 0.044). C2528 again demonstrated an increased risk although this was now weak and borderline non-significant (HR 1.52, 95% CI 0.99–2.31, p = 0.052).

## Discussion

It has been previously demonstrated that two common variants at the *PPARA* locus are associated with opposing risks of development of atherosclerotic vascular disease and myocardial infarction in two separate populations of non-diabetic male subjects taking part in the LOCAT and NPHS2 studies [11]. Individuals with type 2 diabetes are however particularly susceptible to atherosclerotic macrovascular disease, and PPARα activators such as the fibrate group of drugs appear to be particularly beneficial in reducing cardiovascular events in this group of patients [13]. In this study we have confirmed the observation that V162 is associated with a decreased risk and the C2528 variant is associated with an increased risk of cardiovascular disease and that this observation can be extended to individuals with type 2 diabetes. We also found that the association is similar in both male and female individuals. Finally we confirm a recent finding that these variants are associated with opposing influences on age of diagnosis with type 2 diabetes [12], and that the C2528 variant is also associated with significantly higher total cholesterol and calculated LDL cholesterol levels.

**Table 6: Prospective model of *PPARA* variants and non-fatal myocardial infarction risk in the Go-DARTs cohort. A full set of data was available on 1806 individuals, 108 recorded non fatal myocardial infarctions during the period of observation, with a total of 94497.6 months of observation. Both *PPARA* variants were analysed using a co-dominant model.**

| | Hazard Ratio | 95% CI | P |
|---|---|---|---|
| **V162** | 0.31 | 0.10 0.93 | 0.037 |
| **C2528** | 2.77 | 1.34 5.75 | 0.006 |
| **Smoking** | 1.39 | 0.93 2.10 | 0.112 |
| **Gender** | 0.72 | 0.48 1.08 | 0.107 |
| **Age at recruitment** | 1.05 | 1.02 1.07 | <0.001 |
| **Insulin treatment** | 2.56 | 1.69 3.89 | <0.001 |
| **Prevalent angina** | 5.64 | 3.80 8.40 | <0.001 |
| **Prevalent cerebrovascular disease** | 1.29 | 0.67 2.51 | 0.445 |
| **Prevalent myocardial infarction** | 3.90 | 2.60 5.81 | <0.001 |
| **Haplotypes** | | | |
| **L162-G2582** | Ref | | |
| **L162-C2528** | 1.68 | 1.16–2.43 | 0.006 |
| **V162-G2528** | 0.54 | 0.20–1.48 | 0.23 |
| **V162-C2528** | 0.96 | 0.48–1.94 | 0.91 |