The Transthyretin Stabilizing Mutation (T119M) Is Not Associated with Extended Lifespan or Protection Against Vascular Diseases: Analysis of the UK Biobank Cohort

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Introduction

Transthyretin (TTR) and Its Role in Transthyretin-Mediated (ATTR) Amyloidosis

- TTR is a hepatically produced homo-tetrameric protein[1]; its major function is as a transporter of vitamin A and it also has a minor role in the transport of thyroxine[2–4]
- Destabilization of TTR and misfolding into amyloid fibrils can lead to the formation of insoluble deposits in multiple tissues[5–9] that can result in two types of progressive ATTR amyloidosis[10;]
  - Wild-type transthyretin-mediated (wtATTR) amyloidosis: non-hereditary, caused by accumulation of wild-type (wt) TTR amyloid fibrils; predominantly manifests as cardiac symptoms but other systems can be involved[10–13]
  - Hereditary transthyretin-mediated (hATTR) amyloidosis: inherited, caused by accumulation of both mutant and wt TTR amyloid fibrils; multisystem disease that can include sensory and motor, autonomic, and cardiac symptoms[10,14]

TTR Thr119Met (T119M) Mutation

- Pathogenic mutations that lead to hATTR amyloidosis destabilize tetrameric TTR leading to dissociation, the rate-limiting step in amyloid fibril formation[10,15–17]
- *TTR* T119M mutation encodes a thermodynamically and kinetically stabilized TTR protein that increases the stability of TTR tetramers composed of wt or mutant TTR[18,19]
  - Acts by slowing the dissociation of the TTR tetramer, a mechanism that established the therapeutic rationale for the development of small-molecule TTR tetramer stabilizers[20]
- In a Danish cohort[21] of 68,602 participants, the presence of the T119M mutation was associated with extended lifespan and lower risk of cerebrovascular disease

Objectives

- To investigate the potential effect of the *TTR* T119M mutation on vascular disease and mortality in the UK Biobank cohort, and assess whether improved clinical outcomes previously reported for cerebrovascular disease could be replicated

Methods

Study Population

- This analysis includes 337,148 unrelated, white participants from the UK Biobank, a population-based prospective cohort study that recruited ~500,000 participants aged 40–69 years in the UK between 2006 and 2010[22]

T119M Genotyping

- T119M (rs28922981) was imputed with high accuracy (info score = 0.93) from genotyping with the Affymetrix UK Biobank Axiom® array

Data Analysis

- Logistic regression and Cox proportional hazard analysis were used to assess the association between T119M genotype and diagnosis according to International Classification of Diseases, 10th revision of:
  - Vascular disease (I20–I25, I60–I69, or G45)
    - Cardiovascular disease (I20–I25)
    - Cerebrovascular disease (I60–I69 or G45)
      - Ischemic cerebrovascular disease (I64–I69 and G45)
      - Hemorrhagic stroke (I60–I63)
  - Mortality (obtained from linkage to the National Death Registries)
- All statistical models were controlled for age, sex, smoking status, body mass index (BMI), and genetic ancestry via principal component analysis
- Age at death or first vascular diagnosis between T119M carriers and non-carriers were compared using a t-test
- For participants who had a vascular diagnosis and subsequently died, the number of years they survived post-diagnosis was compared using a t-test

Results

Baseline Characteristics

- Allele frequency of T119M within the unrelated, white population from the UK Biobank (n=337,148) was 0.4% (2,499 heterozygotes and 3 homozygotes)
- **Table 1** shows the baseline characteristics of the 337,148 participants included in this study

Table 1. Baseline Characteristics of UK Biobank Study Population by T119M Genotype

	Non-Carriers (CC) (n=334,646)	Carriers (CT or TT) (n=2,502)	P-Value
Mean (SD) age, years	56.9 (8.0)	56.7 (8.0)	0.16
Male, %	46.3	47.0	0.50
Mean (SD) triglycerides, mmol/L	1.8 (1.0)	1.8 (1.1)	0.81
Mean (SD) LDL, mmol/L	3.6 (0.9)	3.5 (0.9)	0.14
Mean (SD) HDL, mmol/L	1.5 (0.4)	1.5 (0.4)	0.36
Mean (SD) BMI, kg/m^2	27.4 (4.8)	27.4 (4.7)	0.87
Mean (SD) C-reactive protein, mg/L	2.6 (4.4)	2.5 (4.4)	0.43
Hypertension, %	22.2	21.0	0.14
Diabetes, %	5.3	5.7	0.40
Smoking, %	45.2	42.8	0.02
Lipid-lowering therapy, %[a]	18.6	17.9	0.43

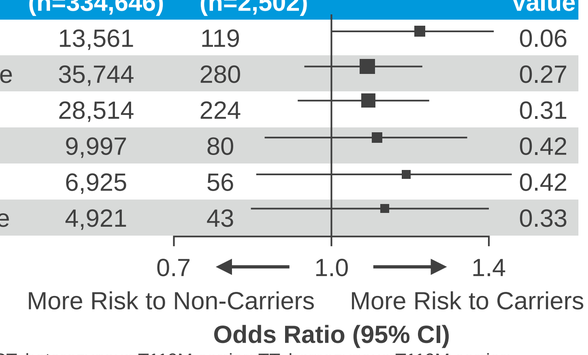
[a]Lipid-lowering therapy defined as self-reported use of atorvastatin, Crestor, eptastatin, ezetimibe, fibrate, fluvastatin, Lipitor, Lescol, niacin, pravastatin, simvastatin, rosuvastatin, velastatin, or Zocor
BMI, body mass index; CC, T119M non-carrier; CT, heterozygous T119M carrier; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation; TT, homozygous T119M carrier

Association of *TTR* T119M Genotype with Death and Vascular Disease (Figure 1)

- Logistic regression analysis that controlled for age, sex, smoking status, BMI, and genetic ancestry found no significant association between T119M genotype and death, all vascular disease, cardiovascular disease, cerebrovascular disease, ischemic cerebrovascular disease, or hemorrhagic stroke

Figure 1. Association of Vascular Disease as a Function of T119M Genotype Using Logistic Regression

Outcome	n Diagnoses Non-Carriers (CC) (n=334,646)	n Diagnoses Carriers (CT or TT) (n=2,502)	P-Value
Death	13,561	119	0.06
All vascular disease	35,744	280	0.27
CV disease	28,514	224	0.31
CVD	9,997	80	0.42
Ischemic CVD	6,925	56	0.42
Hemorrhagic stroke	4,921	43	0.33

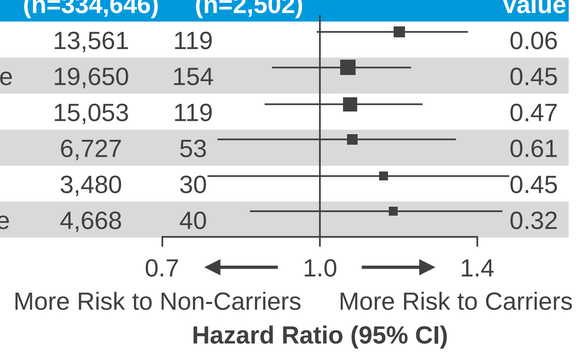


CC, T119M non-carrier; CT, heterozygous T119M carrier; TT, homozygous T119M carrier; CV, cardiovascular; CVD, cerebrovascular disease

- Cox proportional hazard analysis, controlling for age, sex, smoking status, BMI, and genetic ancestry, revealed no difference between T119M carriers and non-carriers in their risk of death or vascular disease, including cardiovascular disease, cerebrovascular disease, ischemic cerebrovascular disease, and hemorrhagic stroke (**Figure 2**)
- There was no association between T119M genotype and time to first vascular disease diagnosis (hazard ratio=1.06, p=0.45) (**Figure 3**)

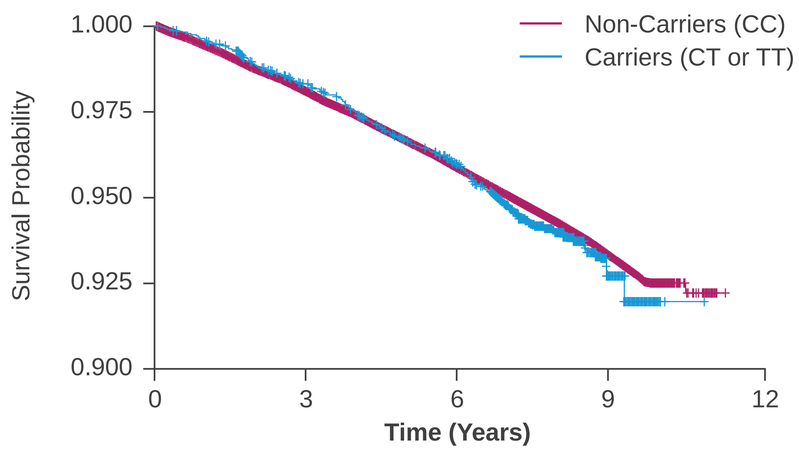
Figure 2. Risk of Vascular Disease as a Function of T119M Genotype Using Cox Proportional Hazard Analysis

Outcome	n Diagnoses Non-Carriers (CC) (n=334,646)	n Diagnoses Carriers (CT or TT) (n=2,502)	P-Value
Death	13,561	119	0.06
All vascular disease	19,650	154	0.45
CV disease	15,053	119	0.47
CVD	6,727	53	0.61
Ischemic CVD	3,480	30	0.45
Hemorrhagic stroke	4,668	40	0.32



CC, T119M non-carrier; CT, heterozygous T119M carrier; TT, homozygous T119M carrier; CV, cardiovascular; CVD, cerebrovascular disease

Figure 3. Time to First Vascular Disease Diagnosis by T119M Genotype

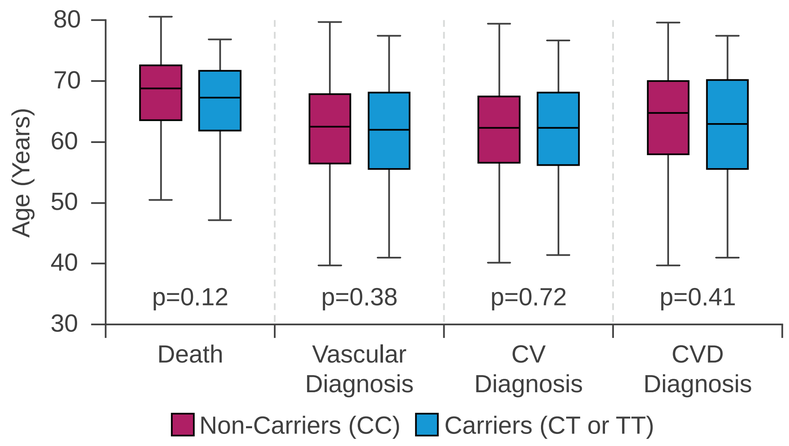


CC, T119M non-carrier; CT, heterozygous T119M carrier; TT, homozygous T119M carrier

Age at Death and Survival Following Diagnosis of Vascular Disease

- Mean age at death from all causes was similar between T119M carriers and non-carriers (p=0.12) and no difference was seen in age at first diagnosis of vascular disease (p=0.38), including cardiovascular disease (p=0.72) and cerebrovascular disease (p=0.41) (**Figure 4**)

Figure 4. Age at Death or Diagnosis by T119M Genotype



CC, T119M non-carrier; CT, heterozygous T119M carrier; TT, homozygous T119M carrier; CV, cardiovascular; CVD, cerebrovascular disease

- Among participants diagnosed with any vascular disease who subsequently died (n=4,180), there was no significant difference between T119M carriers and non-carriers in survival time following vascular disease diagnosis (p=0.82), including cardiovascular disease (p=0.84) and cerebrovascular disease (p=0.41) (**Table 2**)
  - No homozygous (TT) T119M carriers were diagnosed with vascular disease

Table 2. Mean Survival in Years after Diagnosis of Vascular, Cardiovascular, or Cerebrovascular Disease

	Non-Carriers (CC)	Carriers (CT)	P-value
Survival after vascular disease diagnosis, years	5.9	5.7	0.82
Survival after cardiovascular disease diagnosis, years	6.8	7.1	0.84
Survival after cerebrovascular disease diagnosis, years	3.5	2.6	0.41

CC, T119M non-carrier; CT, heterozygous T119M carrier

Conclusion

- In a large, prospective cohort study of 337,148 participants from the UK Biobank, carriers of the *TTR* T119M mutation were not found to be protected against vascular disease, cardiovascular disease, cerebrovascular disease, or death
  - The odds ratios and hazard ratios were >1 (p>0.05) for all analyses, indicating no protective effect of the T119M mutation
  - No significant difference was seen between T119M carriers and non-carriers in their time to death following a diagnosis of vascular disease (including cardiovascular disease and cerebrovascular disease)
- These findings suggest that stabilization of the TTR tetramer via the T119M mutation does not confer protection against vascular disease or death in a general population setting
- Further research is needed to understand the importance of TTR stabilization in ATTR amyloidosis pathogenesis due to the recent advances in therapeutic strategies and the growing interest in the potential earlier intervention in identified carriers of pathogenic *TTR* mutations

Abbreviations: BMI, body mass index; CC, T119M non-carrier; CI, confidence interval; CT, heterozygous T119M carrier; CV, cardiovascular; CVD, cerebrovascular disease; hATTR, hereditary transthyretin-mediated; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation; TT, homozygous T119M carrier; TTR, transthyretin; wt, wild-type; wtATTR, wild-type transthyretin-mediated. **Acknowledgments:** Editorial assistance in the development of the poster was provided by Adelphi Communications Ltd, UK, funded by Alnylam Pharmaceuticals. **Funding:** This study was sponsored by Alnylam Pharmaceuticals.
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