Low plasminogen levels are not associated with an increased risk of arterial thrombosis

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Conflict	Disclosure - if conflict of interest exists
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Director, Officer, Employee	
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ALN-6400:

ALN-6400 is an investigational drug being studied for the treatment of bleeding disorders. ALN-6400 is not approved by any health authority, and the safety and efficacy of ALN-6400 have not been established.

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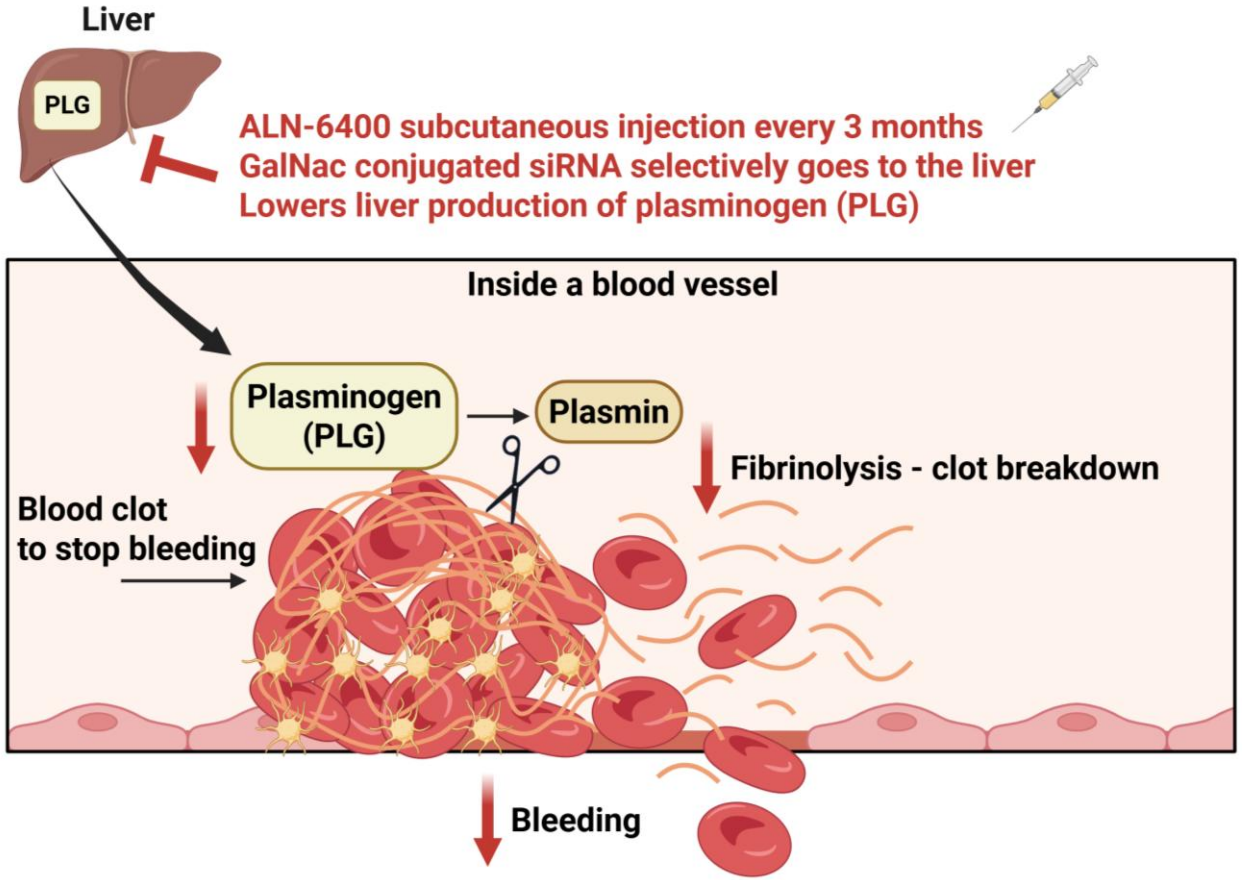
ALN-6400: An Investigational RNAi Therapeutic

- Plasminogen (PLG), which is mainly synthesized in the liver, is central to fibrinolysis
- ALN-6400, an investigational RNA interference (RNAi) therapeutic that lowers the hepatic production of PLG, is being studied for the treatment of bleeding disorders
- Recent analyses suggest that lowering PLG is unlikely to increase the risk of venous thrombosis (Sang et al., Blood 2025; Ivanciu et al., EHA 2025)

Therapeutic Hypothesis



Aim

To examine whether low plasma levels of PLG are associated with myocardial infarction, ischaemic stroke, or arterial thrombosis using human genetic and proteomic data from the UK Biobank

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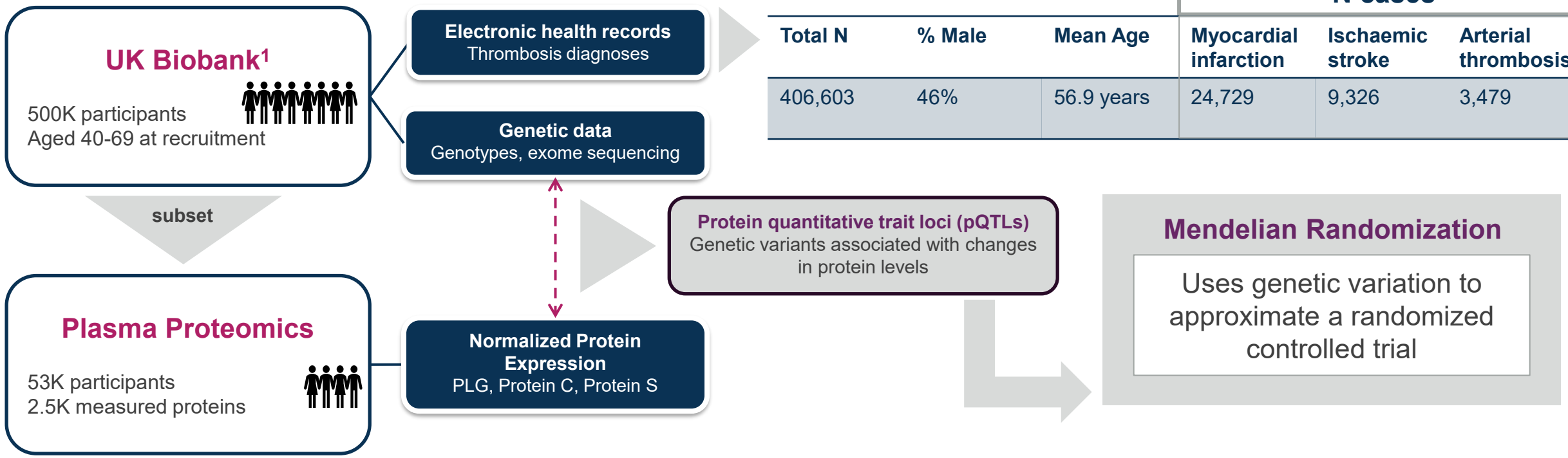
Schematic created with BioRender.com.

Methodology for Computational Analyses in the UK Biobank

Using human genetic and proteomic data from the UK Biobank, we assessed whether low plasma PLG levels were associated with an increased risk of myocardial infarction, ischaemic stroke, and arterial thrombosis

- Linear regression was used to test whether lower PLG levels were **correlated** with arterial thrombosis diagnoses
- Mendelian Randomization (MR) was applied to assess whether lower PLG levels **causally** increases thrombotic risk
- Analyses were repeated with known prothrombotic factors, Protein C and Protein S



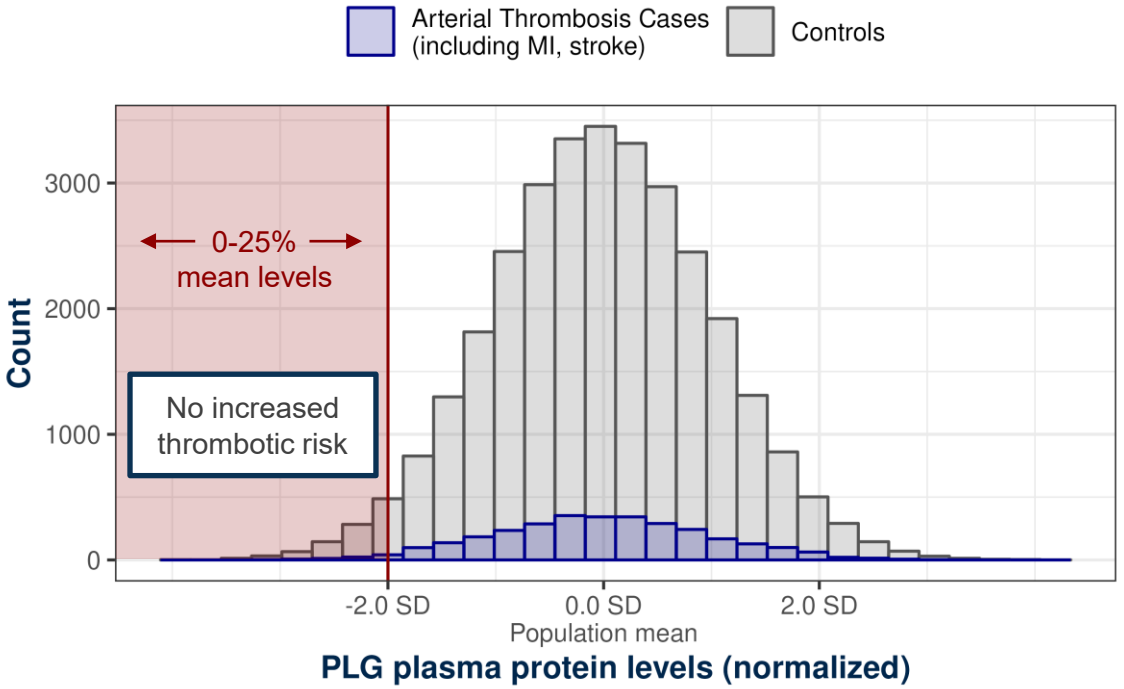
			N cases		
Total N	% Male	Mean Age	Myocardial infarction	Ischaemic stroke	Arterial thrombosis
406,603	46%	56.9 years	24,729	9,326	3,479

PLG, plasminogen.

1. Allen, N. *et al.* UK Biobank: Current status and what it means for epidemiology. *Health Policy and Technology* 2012;**1**:123-126.

Low PLG Levels Are Not Associated With Arterial Thrombosis

PLG level has no correlative or causal relationship with risk for arterial thrombosis



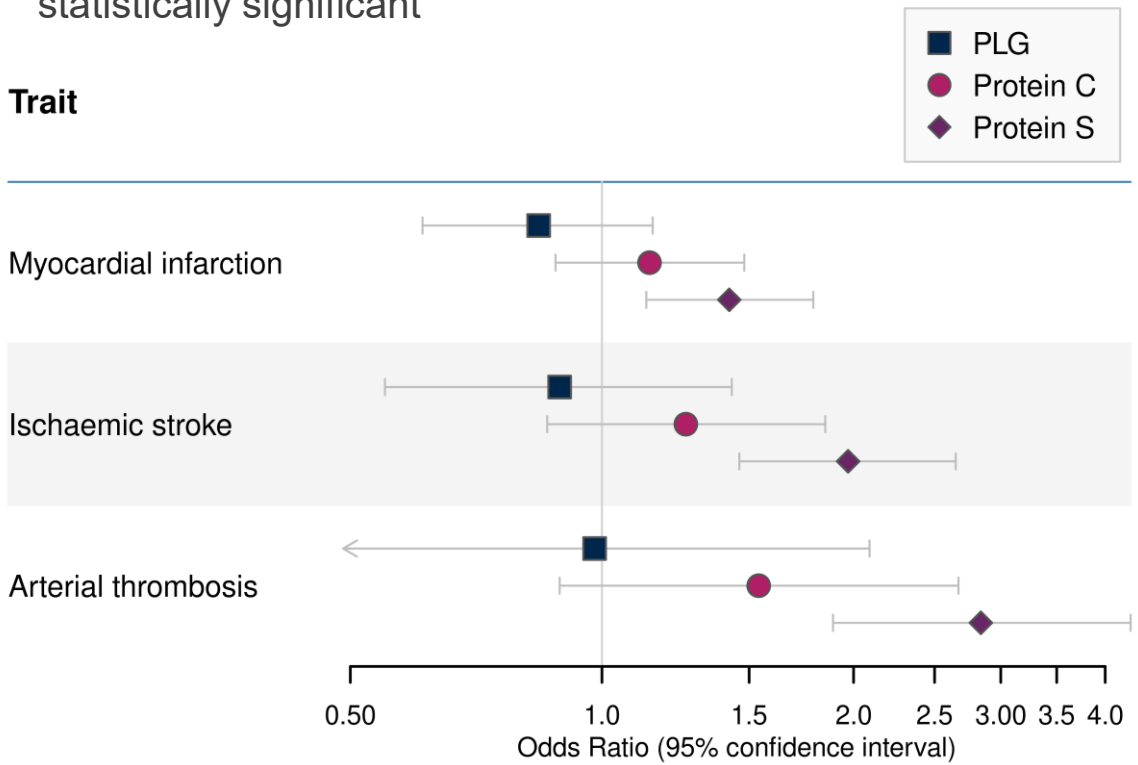
- PLG levels are **not correlated** with arterial thrombosis phenotypes (p>0.05), and those with abnormally low levels* are not at higher risk
- The genetics method Mendelian Randomization confirms **PLG does not have a causal influence** on arterial thrombosis risk

*At least 75% lower than the population mean

MI, Myocardial infarction; PLG, plasminogen.

Increased risk found in positive control

- In contrast to low levels of PLG, individuals with low levels of Protein S are at higher risk for all measured phenotypes (p < 0.006[a])
- Low levels of Protein C trend toward higher risk, although not statistically significant



[a]Bonferroni corrected p-value threshold accounting for 3 proteins, 3 tests each (0.05/9)

Conclusion

- In this analysis of UK Biobank data, low PLG levels were not associated with an increased risk of myocardial infarction, ischaemic stroke, or arterial thrombosis

- Together with prior work, these findings suggest that lowering plasma PLG with an RNAi therapeutic is unlikely to increase the risk of venous or arterial thrombosis and support continued development of ALN-6400 for the treatment of bleeding disorders

InsigHHT

Phase 2 study in Adults with Hereditary Hemorrhagic Telangiectasia (HHT)

HMBeacon

Phase 2 study in Adult and Adolescent Females With von Willebrand Disease (VWD) and Heavy Menstrual Bleeding

PLG, plasminogen; RNAi, RNA interference; InsigHHT: NCT06659640 and HMBeacon: NCT07575308