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Study of stroke prevention in atrial fibrillation

Genetic determinants of dabigatran plasma levels and their relation to bleeding

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Background

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- Dabigatran etexilate is effective and safe in prevention of stroke in AF patients compared with warfarin

- Dabigatran etexilate is an oral prodrug that is rapidly converted by esterases (CES1) to the active agent dabigatran

- We hypothesized genetic factors are responsible for some of the inter-individual variability in dabigatran exposure

RE-LY Trial

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- AF patients with at least one additional RF for stroke
- 18,113 patients with median follow-up of 2.0 years
- Randomized trial of two fixed doses of dabigatran etexilate (110 and 150 mg bid) and open-label warfarin
  - 110 mg as effective as warfarin
  - 150 mg superior to warfarin
  - Both doses had lower minor and major bleeds

Methods Summary

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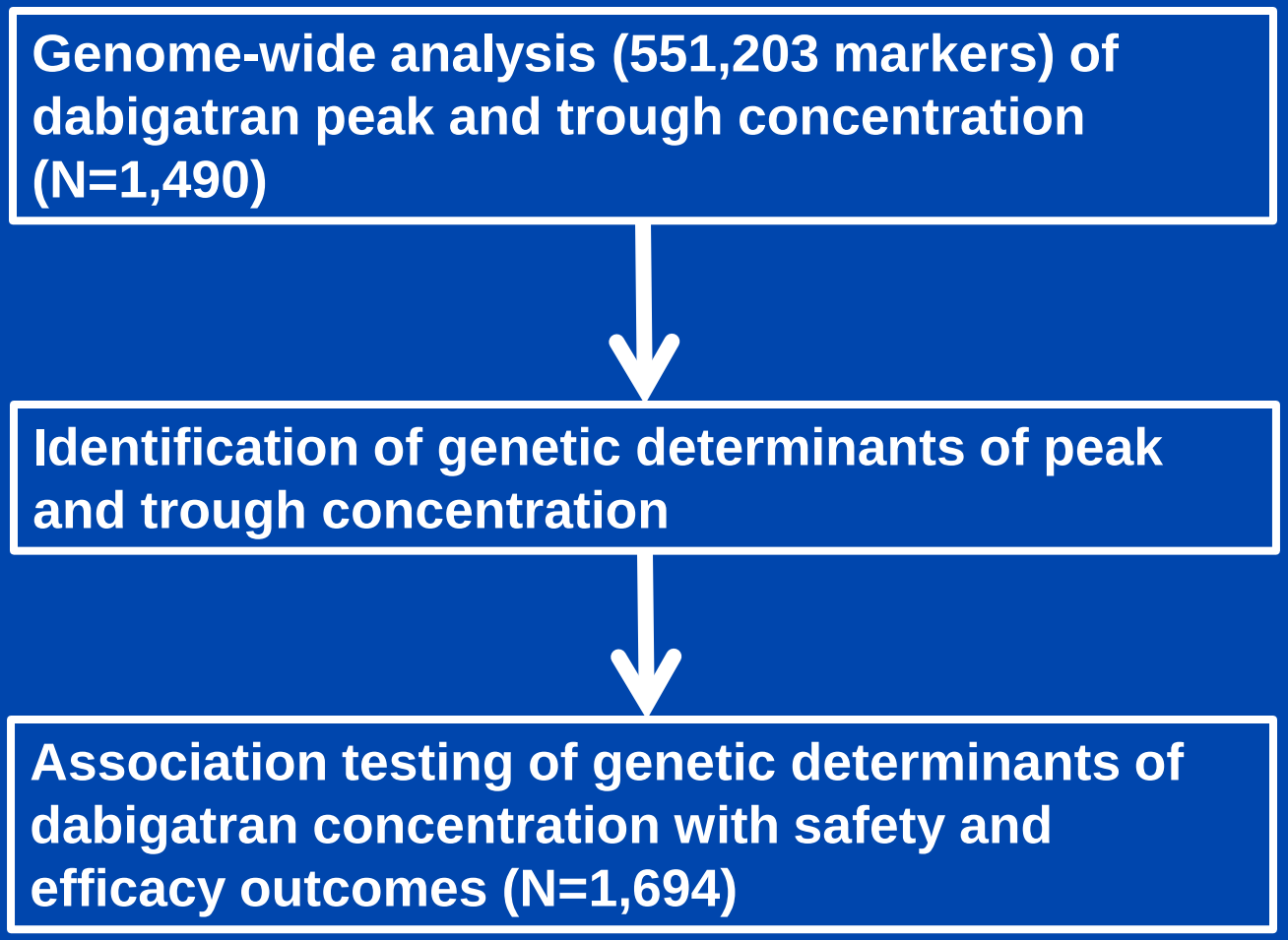

Methods

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- Primary efficacy endpoint defined as stroke or systemic embolism
- Primary safety endpoint define as any bleeding, minor and major
- 1,694 dabigatran etexilate-treated RE-LY participants of European ancestry successfully genotyped
  - Illumina Human610-quad beadchip (551,203 SNPs passed QC)
  - 807 warfarin-treated participants also genotyped
- 1,490 participants also had peak (1 to 3H) and trough concentrations measured by HPLC-MS/MS

Study Population

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	Warfarin	Dabigatran 110 mg	Dabigatran 150 mg
Baseline characteristics			
N	807	849	845
Age	72.2 (7)	71.7 (7.5)	71.9 (7.6)
Female (%)	273 (33.8%)	259 (30.5%)	272 (32.2%)
BMI (Kg/m^2)	29.4 (5.6)	28.9 (5.7)	29.2 (5.3)
CHADS2	2.0 (1.1)	2.0 (1.2)	2.0 (1.1)
History of Stroke (%)	83 (10.3%)	91 (10.7%)	77 (9.1%)
History of Diabetes (%)	158 (19.6%)	178 (21.0%)	159 (18.8%)
Aspirin Use (%)	228 (28.3%)	265 (31.2%)	234 (27.7%)
Dabigatran concentration			
Number with measurements (%)	-	752 (88.6%)	738 (87.3%)
Trough Concentration (ng/mL)	-	73 (48)	105 (72)*
Peak Concentration (ng/mL)	-	156 (94)	220 (133)*
Events			
Ischemic Stroke or Systemic Emboli (%)	12(1.5%)	15(1.8%)	17(2.0%)
Any Bleed (%)	325(40.3%)*	289(34.0%)	298(35.3%)
Major Bleed (%)	45(5.6%)	49(5.8%)	52(6.2%)
Minor Bleed (%)	306(37.9%)*	270(31.8%)	275(32.5%)

Peak and Trough Concentration GWAS

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SNP	Chromosome	Position (bp)	Locus	Function	MAF (Allele)	Fold Change per Minor Allele (95%CI)	P-Value
Peak Concentration							
rs4148738	7	87000985	ABCB1	Intron	0.45 (G)	1.12 (1.08-1.17)	8.2×10^{-8} ←
rs8192935	16	54419295	CES1	Intron	0.33 (A)	0.88 (0.84-0.92)	3.2×10^{-8} ←
Trough Concentration							
rs4580160	16	54326141	CES1P2	Intron	0.30 (A)	0.88 (0.84-0.92)	1.7×10^{-8}
rs2244613	16	54402110	CES1	Intron	0.18 (C)	0.85 (0.81-0.90)	1.2×10^{-8} ←

- MAF: Minor allele frequency
- Linear regression with adjustment for dose, age, sex, BMI, CrCl, PPI, P-gp inhibitor use and first 10 principal components
- Additive genetic model (gene-dose effect)
- Significance set at $P < 9 \times 10^{-8}$

ABCB1 Locus – Peak Concentration

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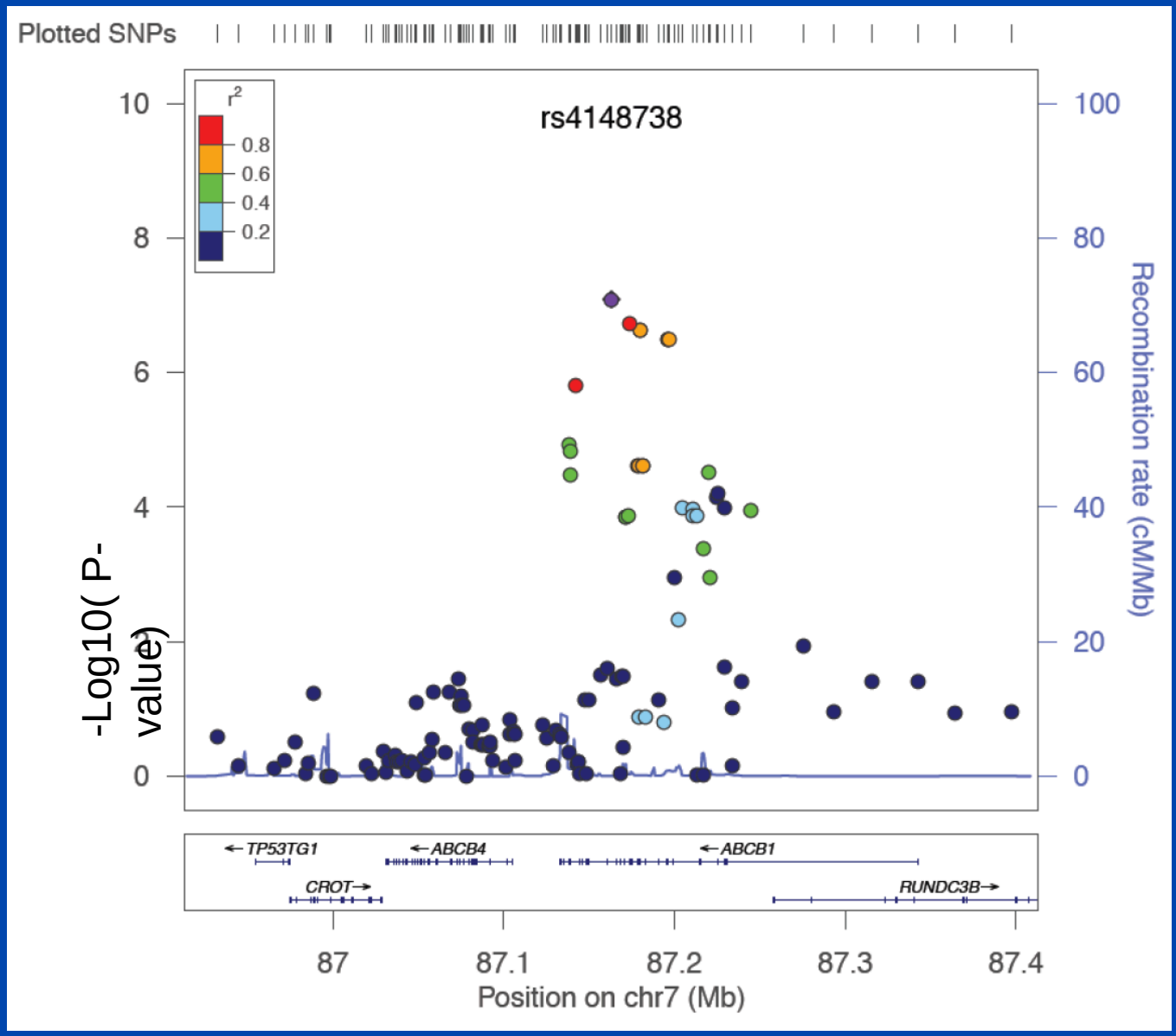

CES1 Locus – Peak Concentration

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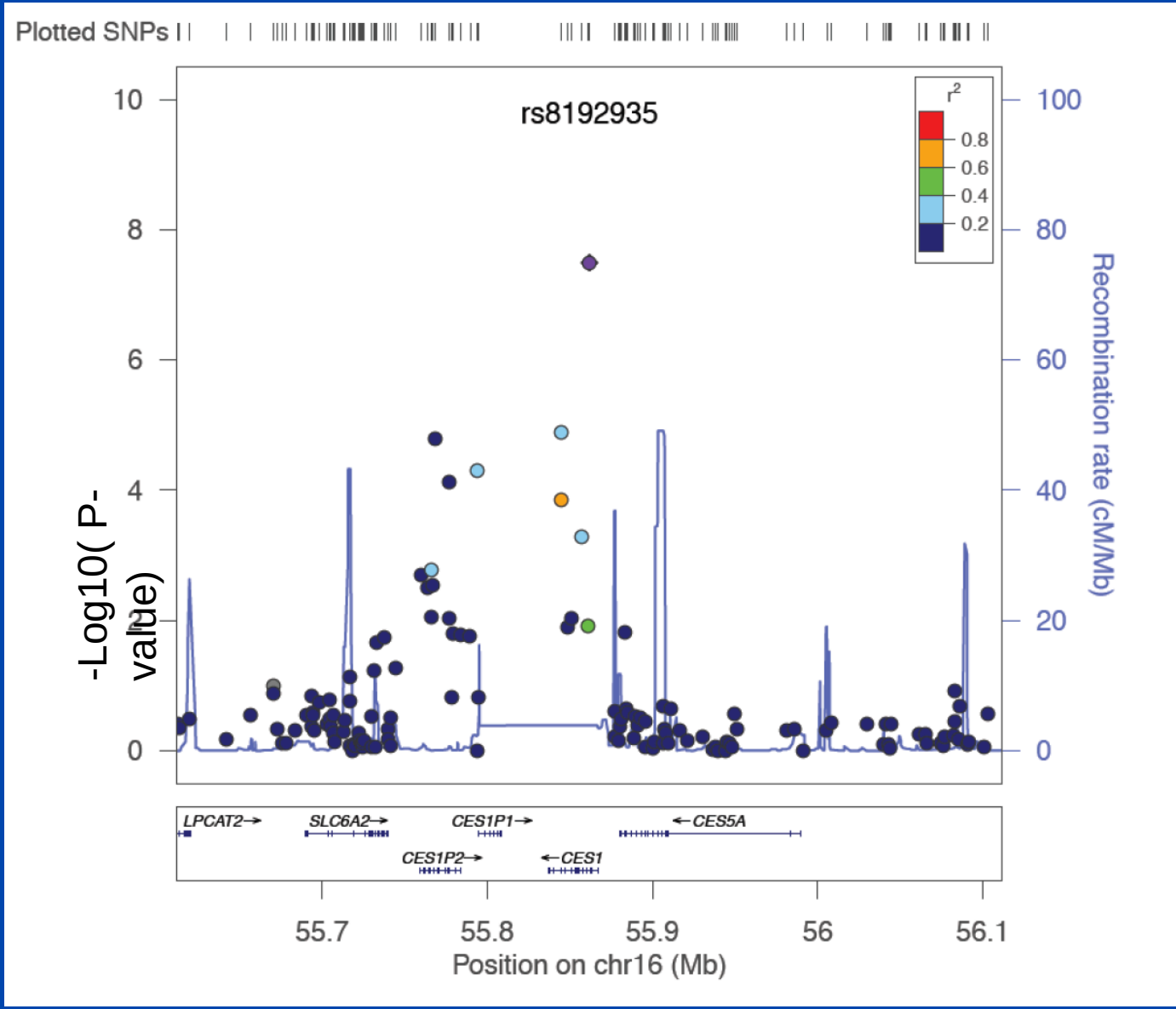

CES1 Locus – Trough Concentration

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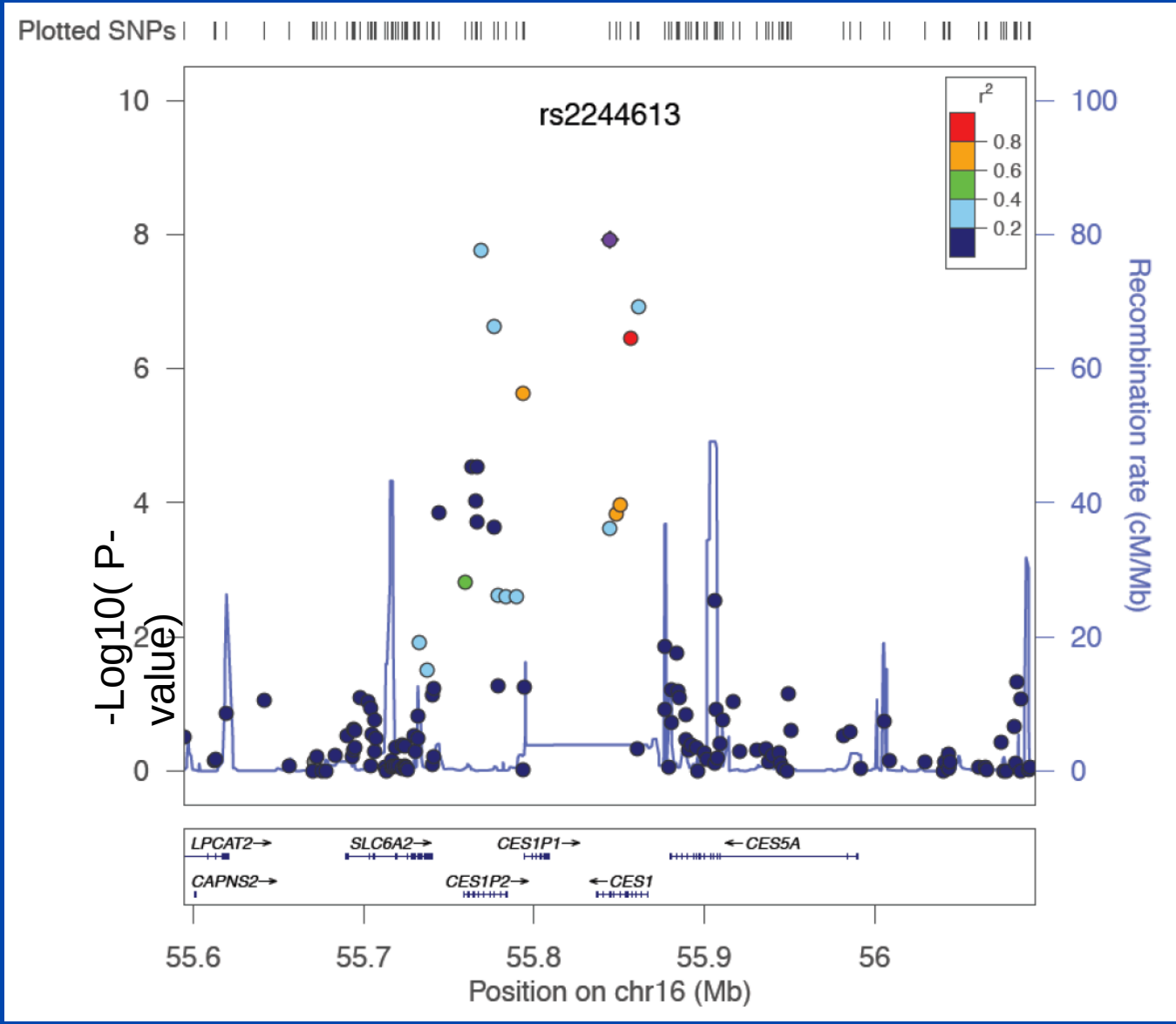

Association with Events

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Event	rs4148738 (*ABCB1*; Peak concentration) OR (95%CI) *	P	rs8192935 (*CES1*; Peak concentration) OR (95%CI) *	P	rs2244613 (*CES1*; Trough concentration) OR (95%CI) *	P
Ischemic Stroke or Systemic embolism	0.88(0.53-1.46)	0.62	0.76(0.43-1.34)	0.34	0.70(0.33-1.47)	0.34
Any Bleeding	0.94(0.82-1.09)	0.44	0.89(0.76-1.03)	0.13	**0.67(0.55-0.82)**	**$7x10^{-5}$**
Major Bleeding	1.14(0.85-1.52)	0.40	0.88(0.64-1.21)	0.44	0.66(0.43-1.01)	0.06
Minor Bleeding	0.94(0.81-1.09)	0.38	0.89(0.76-1.05)	0.17	**0.70(0.57-0.85)**	**$4x10^{-4}$**

- *: Odds ratio per minor allele (gene-dose effect)
- Logistic regression with adjustment for dose, age, sex, CHADS2, ASA, CrCl and first 10 principal components
- Significance set at $P < 0.05$

Survival Analysis

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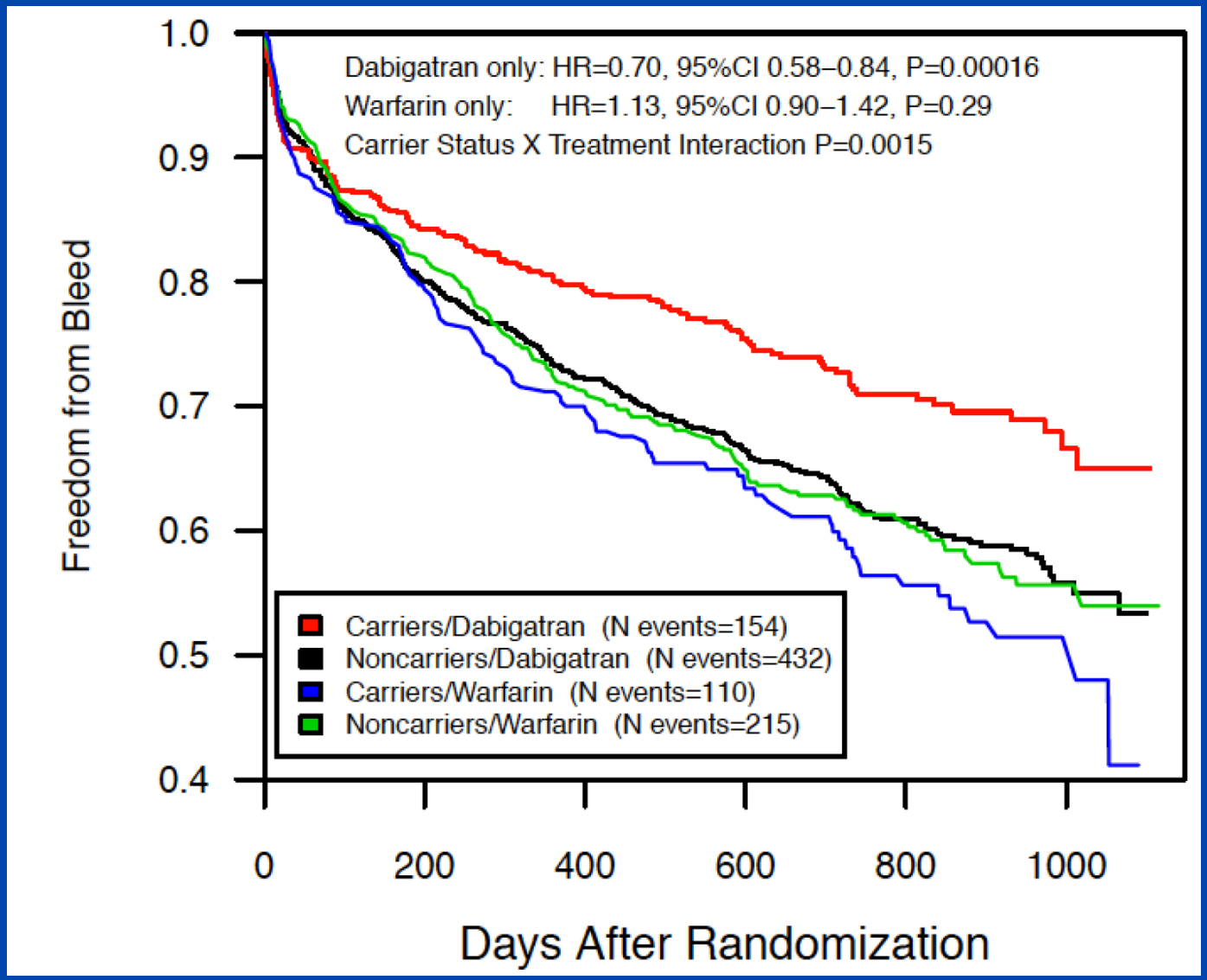
Freedom from bleed according to rs2244613 carrier status



Conclusions

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- *ABCB1* and *CES1* loci are associated with dabigatran concentration
  - Dabigatran etexilate is a substrate of ABCB1
  - CES1 is responsible for the biotransformation of dabigatran etexilate into dabigatran
- 32.8% of Europeans are carriers of the *CES1* SNP rs2244613
  - Each minor allele is associated with 15% decrease in trough concentration
  - Carriers have 27% decrease in relative risk of bleed
  - 14% decrease in relative risk of bleed for low vs high dose of dabigatran etexilate in the parent study
- No association with efficacy – but modest statistical power

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Thanks!

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