Haemostatic gene factors and risk of vascular events in Russian patients with stable coronary artery disease: the results of 4 years follow-up.

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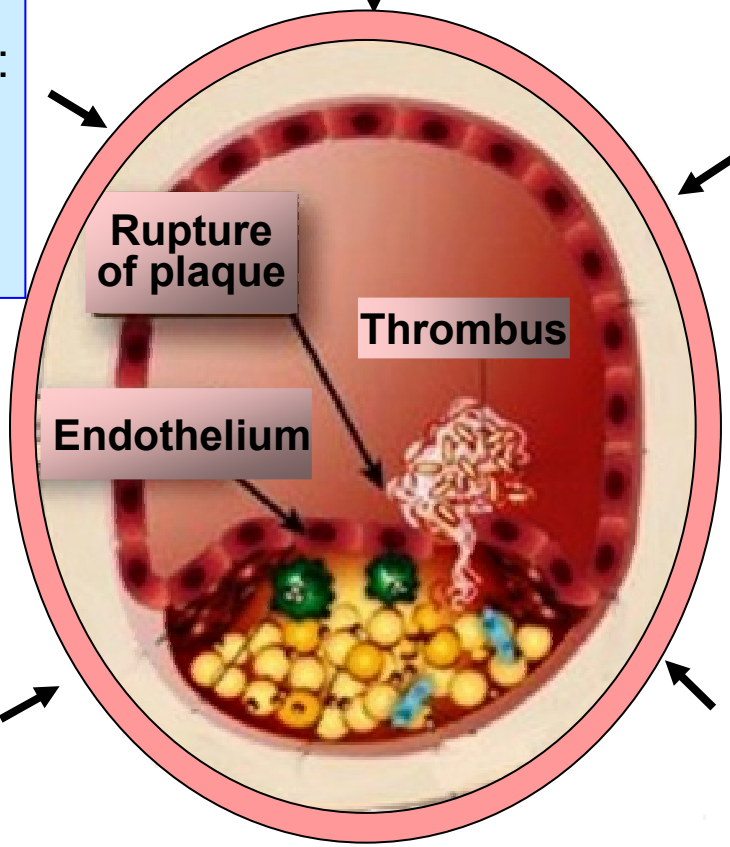
RISK FACTORS FOR ATHEROTHROMBOTIC VASCULAR DISEASE

Conventional risk factors:
Age, male sex, smoking, hypertension, diabetes mellitus, hypercholesterolemia, obesity, etc…

History of atherothrombotic disease:
- ACS,
- Stroke / TIA,
- Stable angina,
- Intermittent claudication

Inflammation and haemostatic factors:
- Fibrinogen,
- Factor VII,
- D-Dimer
- CRP,
- PAI-1,
- Homocystein



Asymptomatic vascular changes:
- ↑ Intima-media thickness
- ↓ Ankle-brachial index

Genetic factors:
- **Coagulation**
- Endothelial function
- Lipid metabolism

Atherosclerosis is a complex multifactorial and polygenic disorder with thrombosis playing a key role in its acute and chronic manifestations. The linking between haemostatic factors and cardiovascular events has been well established. Certain genetic polymorphisms may have a potential effect on clot formation, however, their predicative role is not well defined.

AIM OF THE STUDY

- **to assess the prevalence and potential utility of emerging haemostatic gene factors for long-term cardiovascular events prediction in Russian population of patients with stable coronary artery disease**

STUDY DESIGN

Inclusion

1.Outpatients aged≥ 45

2.Documented CAD

- stable angina, Class II – III
- unstable angina or MI > 2 months ago
- PCI/CABG > 2 months ago

3. Therapy:

- antiplatelets
- statins,
- ß-blockers,
- ACE inhibitors

Risk profile assessment

1. Classic risk factors

2. Cerebrovascular disease (carotid US, CT/MRI if needed)

3. Peripheral arterial disease (US, ABI)

4. Genotyping (haemostatic polymorphisms)

End points

(follow-up ~48 months)

1.Thrombotic events:

- CV death,
- nonfatal ACS,
- stroke/TIA,
- peripheral thrombosis

2.Revascularization in any affected arterial area

STUDY POPULATION
(risk factors profile)

Classic CV risk factors were common in pts with stable symptomatic CAD

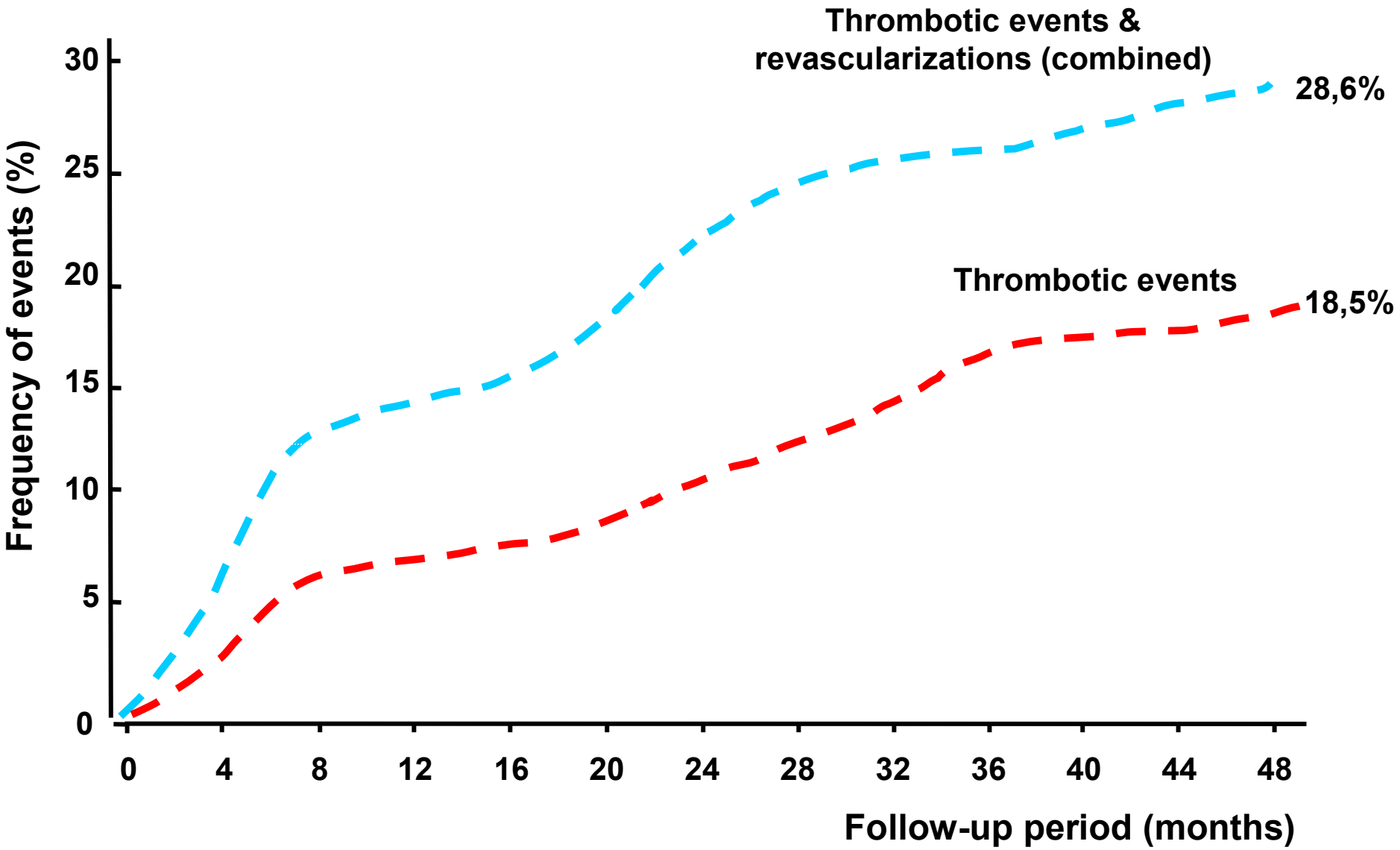
Gender (male/female), n	280 (209/71)
Age, yrs (M±m)	61± 9
Arterial hypertension, n (%)	239 (85,4%)
Hyperlipidemia*, n (%)	217 (77,5%)
Smoking • in history, n (%) • continued, n (%)	 100 (35,7%) 65 (23,3%)
Obesity (BMI> 30 kg/m^2), n (%)	87 (31,1%)
Diabetes mellitus, n (%)	56 (20%)
Atrial fibrillation, n (%)	16 (5,7%)
Serum creatinine, mg/dl (M±m)	1,07 ± 0,01

* Serum cholesterol > 5,2 mmol/l and/or current intake of lipid lowering drugs

STUDY POPULATION
(affected vascular beds)

Coronary artery disease (inclusion criteria)	**280 (100%)**
• Stable angina, functional class II – III	181 (64,6%)
• ACS > 2 months ago	169 (60,4%)
• PCI / CABG > 2 months ago	166 (59,3%)
Coexisting with cerebrovascular disease (CVD)	**64 (22,9%)**
• Ischemic stroke / TIA > 2 months ago	34 (13,2%)
• Carotid artery stenosis > 50%	37 (12,1%)
• Carotid surgery/angioplasty > 2 months ago	10 (3,6%)
Coexisting with peripheral arterial disease (PAD)	**51 (18,2%)**
• ABI <0,9	50 (17,9%)
• Intermittent claudication, Fontaine stage II-III	31 (11,1%)
• History of lower limb amputation	1 (0,35%)
• Peripheral surgery / angioplasty > 2 months ago	4 (1,4%)

FOUR-YEARS EVENT CURVES FOR PATIENTS WITH STABLE CAD

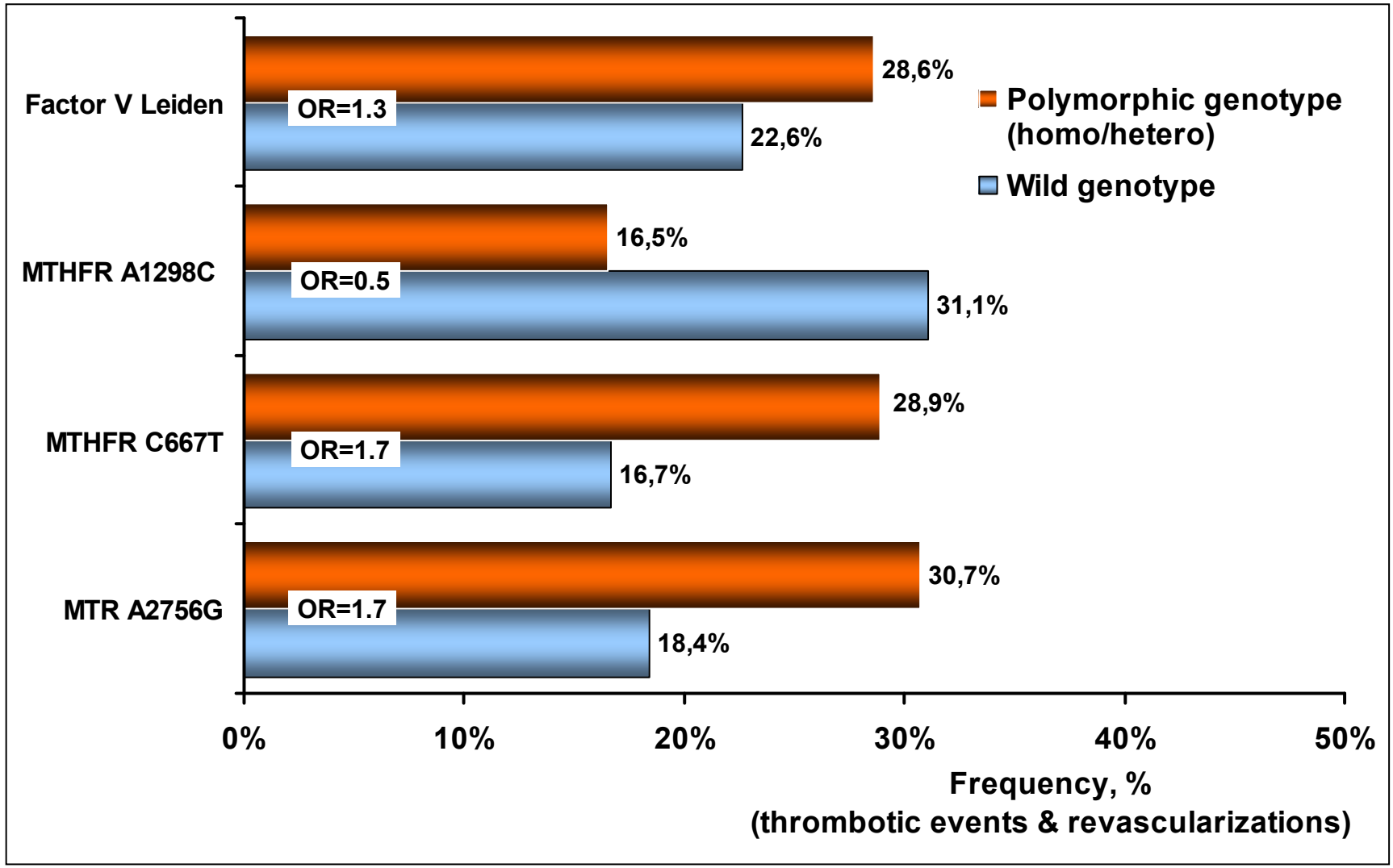


HAEMOSTATIC GENE POLYMORPHISMS ANALYSED IN THE STUDY

Polymorphism	Effects on phenotype	Frequency, %	
		Total	Hetero / homozygous
Factor V Leiden G 1691A	Activated protein C resistance	4,6	4,2/0,4
Platelet membrane proteins			
GP IIIa T1565C	↑ sensitivity to platelet aggregation	55,3	39,8/15,5
P2Y12 G18T	Clopidogrel resistance (?)	29,6	22,3/7,3
P2Y12 G36T	Clopidogrel resistance (?)	28,7	19,7/9
Enzymes involved in metabolism of homocysteine (Hcy)			
MTHFR C677T	↓MTHFR activity, ↑ Hcy level	43,9	31,7/12,2
MTHFR A1298C	↓ MTHFR activity, Hcy level?	56,5	43,6/12,9
MTR A2756G	MTR activity ? Hcy level ?	38,8	7,3/31,5
MTRR A66G	↓ MTRR affinity to MTR, Hcy level?	76,5	33,8/41,8
TCN C667G	↓ TCN affinity to B_{12}, Hcy level?	61,1	43,6/17,5

HEMOSTATIC GENE POLYMORPHISMS AND RISK OF VASCULAR EVENTS

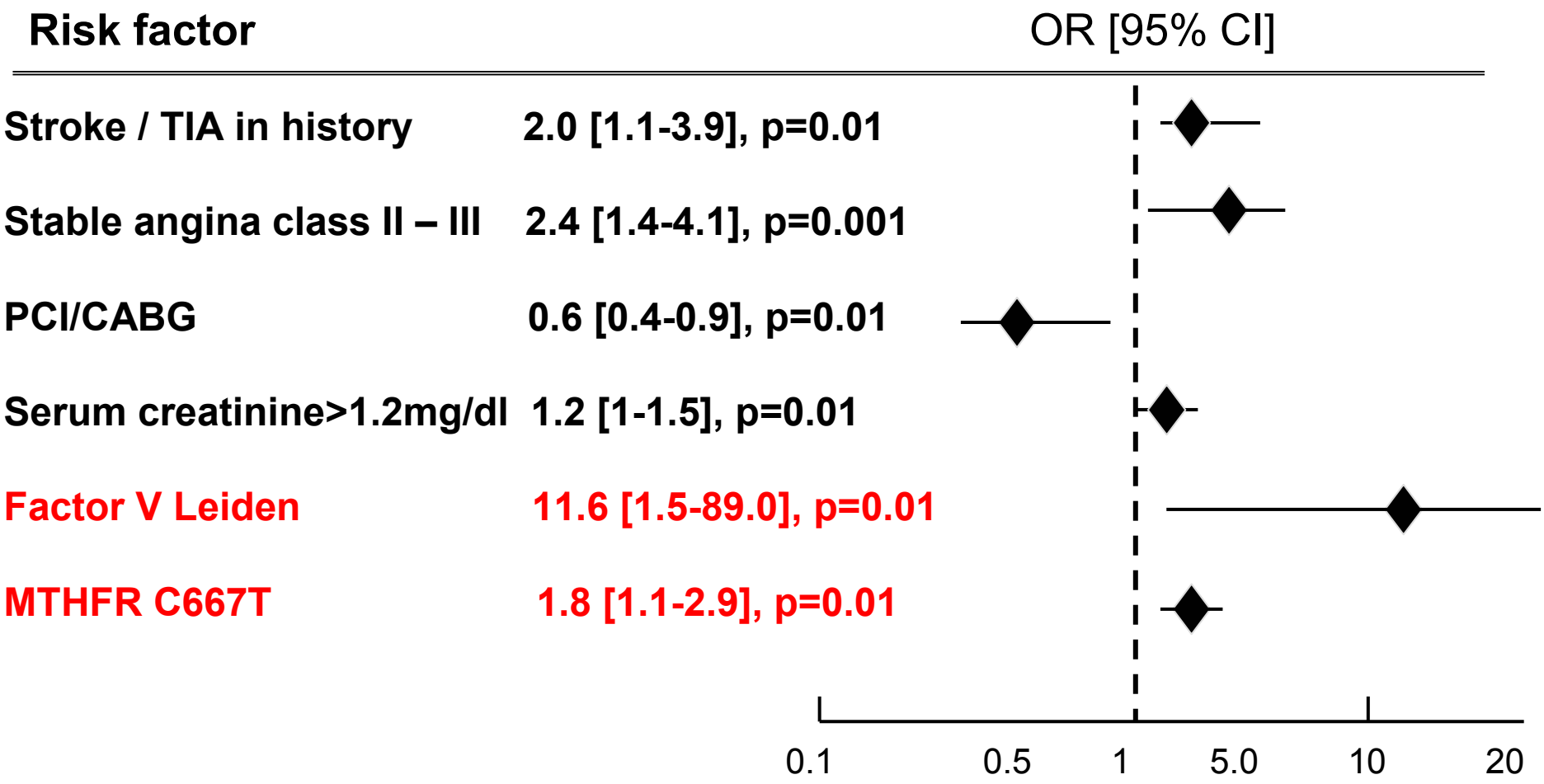
(univariate analysis)



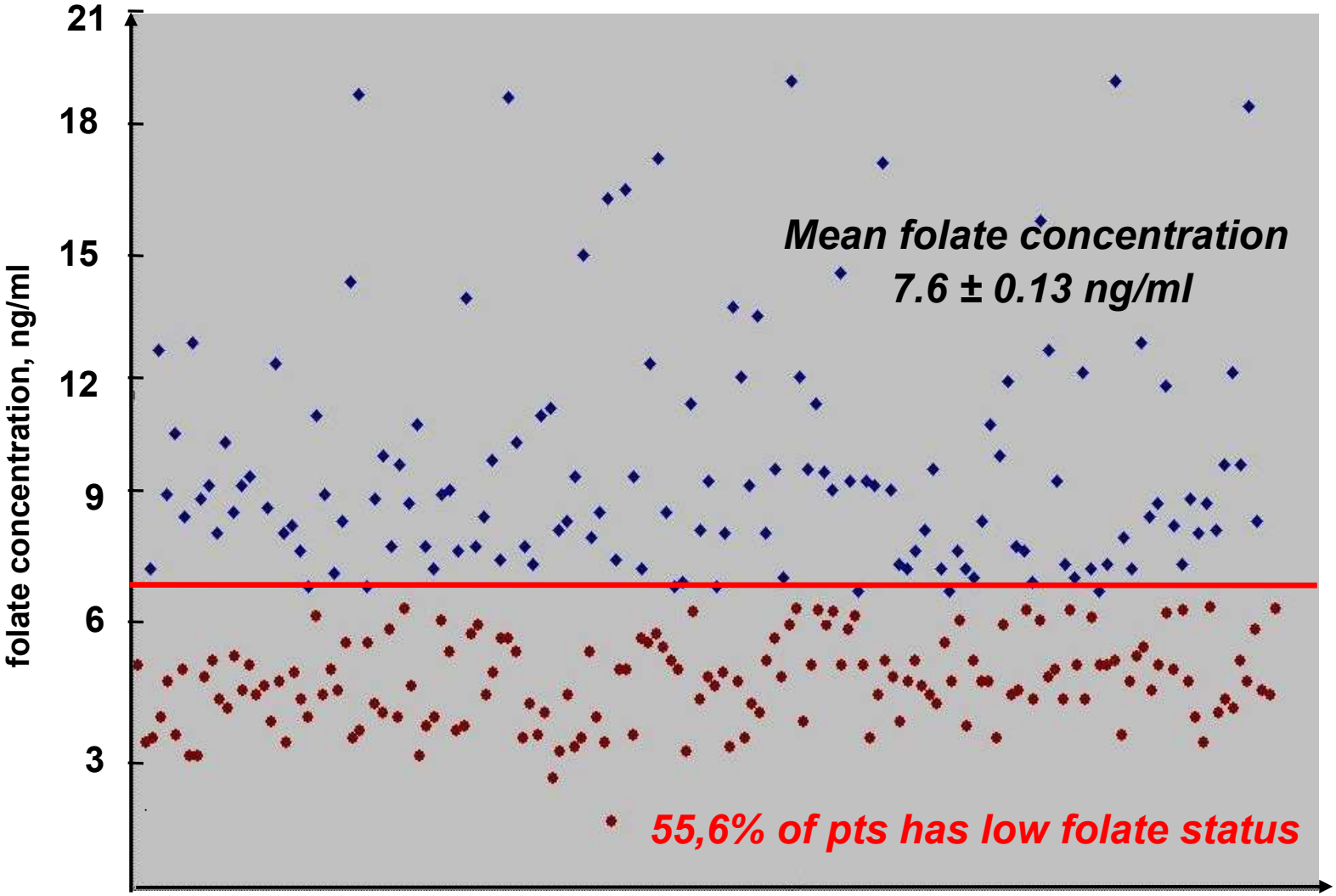
The other polymorphisms are not associated with risk of vascular events

PREDICTORS OF VASULAR EVENTS

(Cox proportional hazards model)



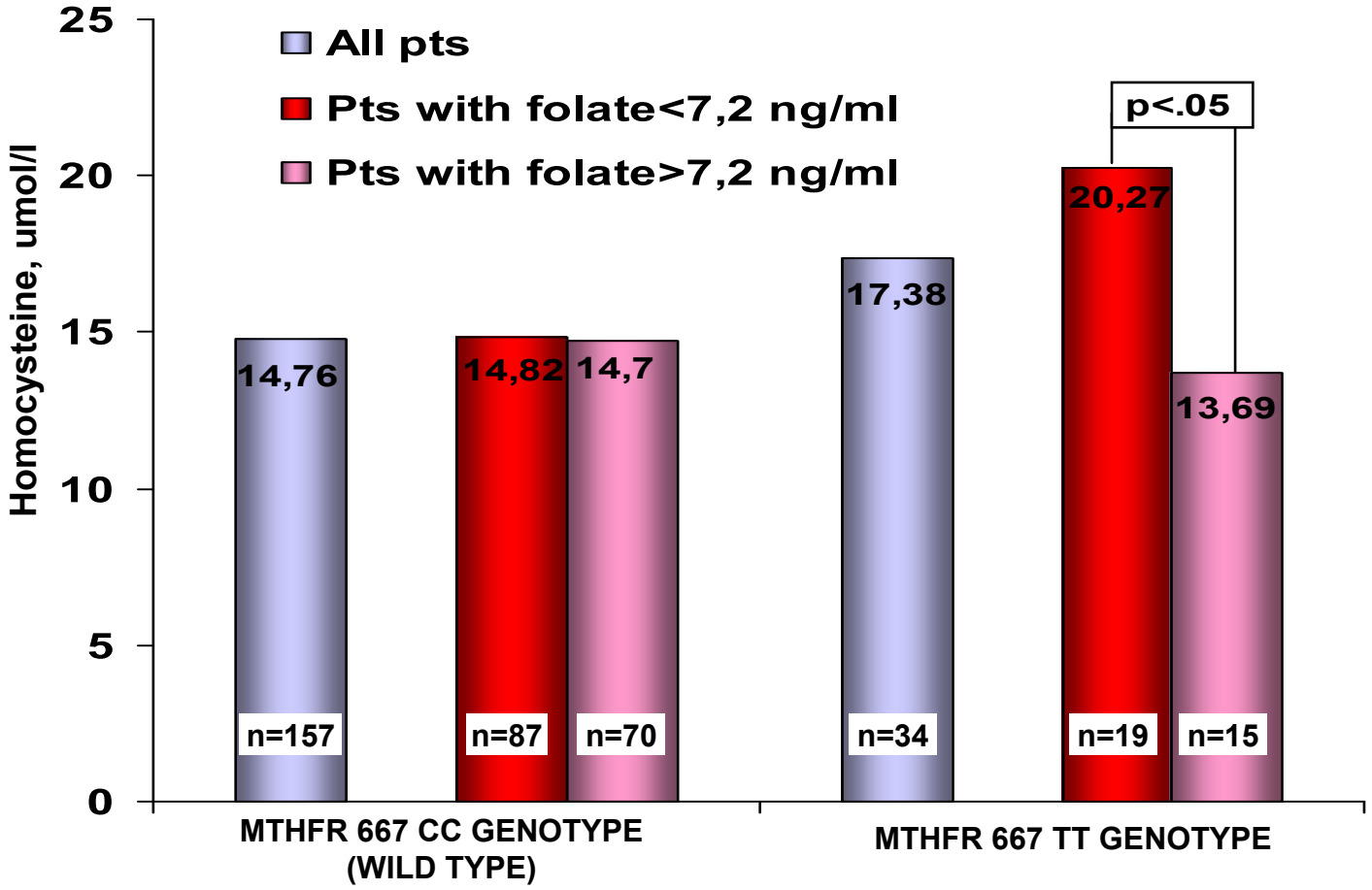
FOLAT STATUS OF PTS WITH CAD



Possible implications of folat depletion:

- Folate food fortification program is not widely accepted in Russian Federation
- Alcohol abuse is common in Russian Federation

PLASMA HOMOCYSTEINE CONCENTRATION ACCORDING TO FOLATE STATUS AND MTHFR C667T GENOTYPE IN PATIENTS WITH CAD



- Mean Hcy concentration 15.0 ± 0.2 umol/l
- MTHFR C667T polymorphism is associated with raised plasma Hcy only in the setting of low folate status.

CONCLUSION

- Both Leiden mutation and MTHFR C677T polymorphism were independently associated with increased risk of vascular events in Russian population of patients with stable coronary artery disease.
- More than ½ of Russian patients with CAD had low plasma folate concentration.
- The risk increase conferred by MTHFR C677T is probably mediated by folate depletion.