A GENETIC MARKER OF HYPERURICEMIA PREDICTS CARDIOVASCULAR EVENTS IN A META-ANALYSIS OF THREE COHORT STUDIES IN HIGH RISK PATIENTS

Testa A[a], Prudente S[b], Leonardis D[a], Spoto B[a], Sanguedolce MC[a], Parlongo RM[a], Tripepi G[a], Rizza S[c], Mallamaci F[a], Federici M[c], Trischitta V[b], Zoccali C[a]

a CNR-IFC, Reggio Calabria, Italy
b IRCCS Casa Sollievo della Sofferenza Mendel Laboratory, San Giovanni Rotondo, Italy
c Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

INTRODUCTION

Whether hyperuricemia is causally implicated in atherosclerotic complications is perhaps one among of the most vexed questions in cardiovascular medicine and there is no randomized clinical trial based on clinical end-points testing the hypothesis that reducing serum uric acid may reduce cardiovascular events in high risk patients. The strongest genetic marker of uric acid levels, the rs734553 SNP in the GLUT9 urate transporter (Fig.1) gene, predicts progression to kidney failure in CKD patients and associates with systolic BP and carotid intima media thickness. We used the risk allele (T) of this genetic polymorphism as an unconfounded research instrument to further explore the link between uric acid and cardiovascular events (Mendelian randomization approach) in a meta-analysis of three cohort studies enrolling high risk patients. The three cohorts were formed by patients with Chronic Kidney Disease (CKD, MAURO study cohort), type-2 diabetes with coronary artery disease (Gargano Heart Study, GHS) and myocardial infarction (MI, Tor Vergata Atherosclerosis Study, TVAS).
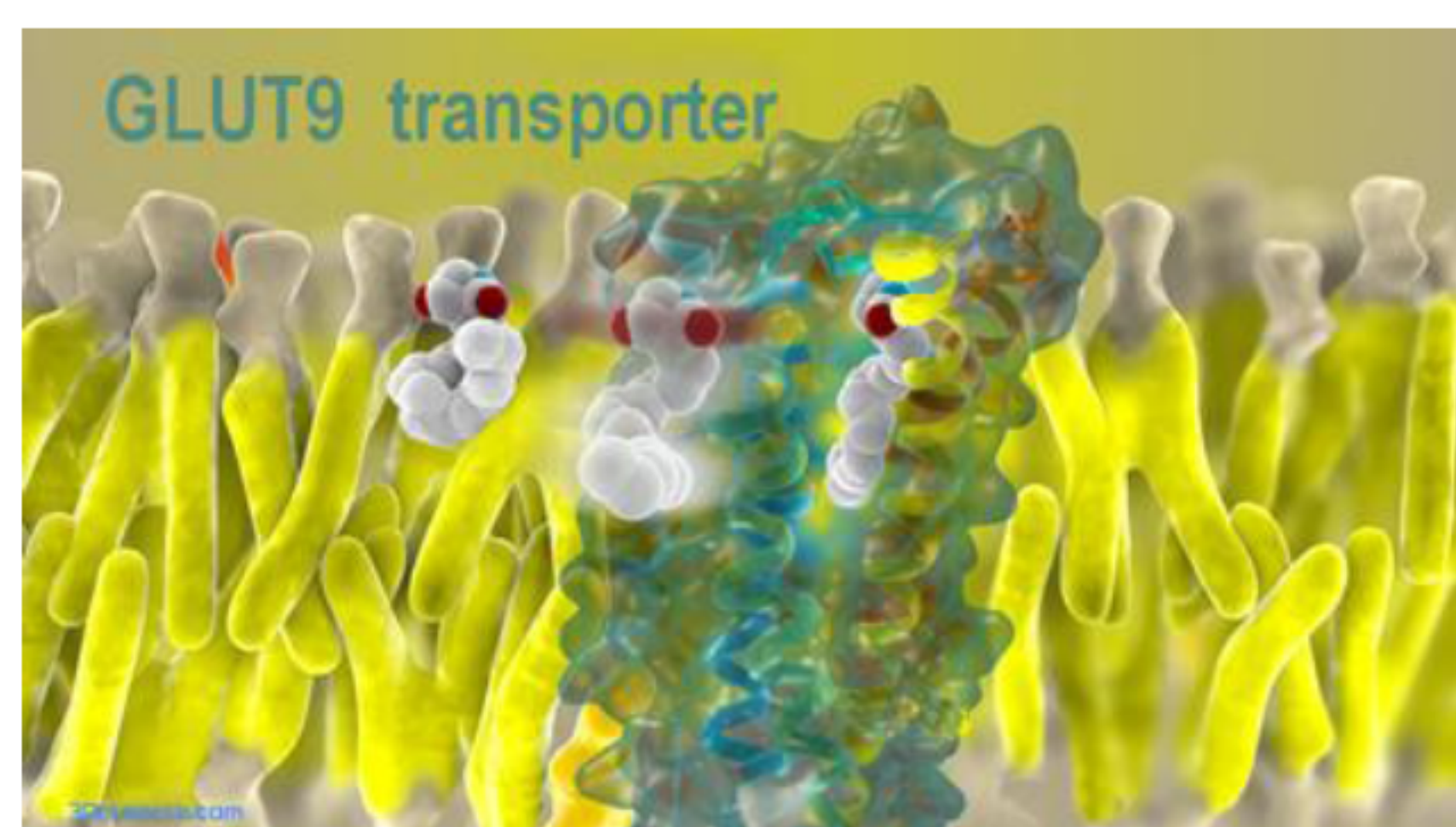

GLUT9 transporter

FIG.1

METHODS

The three cohorts included 755 G2-G5 CKD patients (MAURO); 353 subjects with type 2 diabetes and coronary artery disease (GHS) and 119 patients with severe coronary heart disease and MI (TVAS). The major clinical end point was a composite end point including cardiovascular death or nonfatal stroke, and nonfatal MI. Genotyping was performed by Real Time PCR (Fig. 2). The meta-analysis was performed by the random effects approach.

FIG.2

RESULTS 1

The average mean follow-up was 31 months (range, 0.3–49 months) in MAURO, 65 months (range 1–119) in GHS and 30.6 months (range 1–37) in TVAS. During follow-up, 117 CV events occurred in MAURO, 72 in GHS and 33 in TVAS.
Of the 12 SNPs investigated, the rs11085735 of Keap1 gene resulted to be associated with CV events. The analysis of Hardy-Weinberg equilibrium in the three cohorts showed that there was no deviation from the expected genotypic frequencies in GHS (GG: 10%; GT: 38%; TT: 52%, χ^2=1.8, P=0.18) and TVAS individuals (GG: 9%; GT: 38%; TT: 53%, χ^2=0.5, P=0.47) whereas a slight deviation was found in the MAURO study cohort (GG: 8%; GT: 35%; TT: 57%, χ^2=4.3, P=0.04). No difference for demographic and biochemical risk factors was found between GG and AA/AG patients, according to a dominant model (Mendelian Randomization) (table 1).
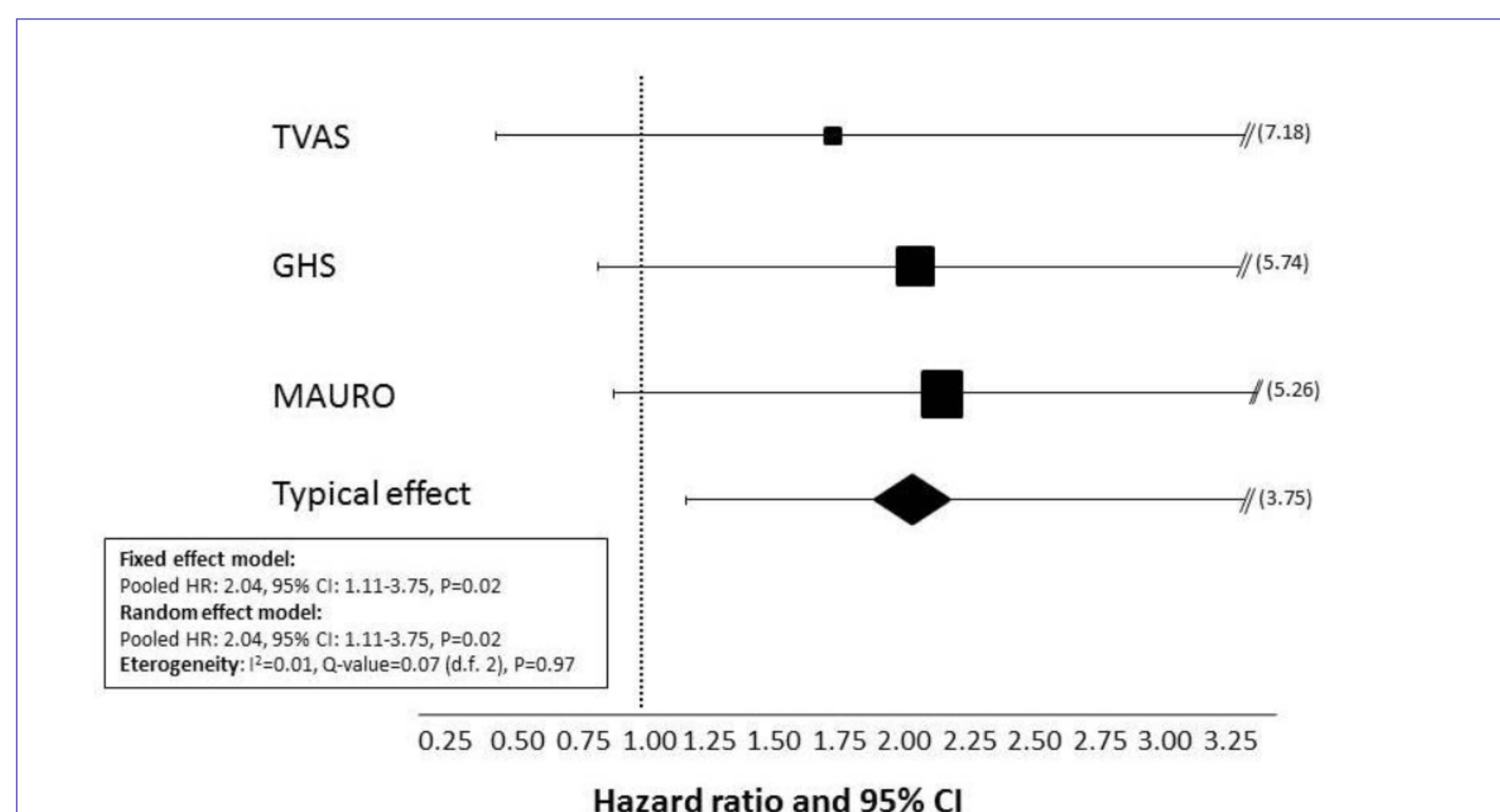
RESULTS 2

In separate analyses in the three cohorts, the incidence rate of CV events was higher in patients with the rs734553 risk (T) allele (TT/GT) than in those without (GG patients) and the HR in the three cohorts was very similar ranging from 1,72 to 2,14 with no heterogeneity (I^2=0.01) among the three cohorts (fig.3). The meta-analytical estimate in the three cohorts (total number of patients, n=1227; total CV events, n=222) of the risk for cardiovascular events in TT/GT patients was twice higher (pooled HR: 2.04, 95% CI: 1.11-3.75, P=0.02) than in GG homozygotes.

	MAURO study (n=755)	GHS (n=353)	TVAS (n=119)
Age (years)	62±11	64±8	62±10
Male sex (%)	60%	68%	81%
Diabetes (%)	35%	100%	14%
Smoking (%)	50%	48%	74%
BMI (kg/m2)	28±5	30±5	28±4
Diagnosis of Gout (%)	5%	3.6%	NA
Systolic BP (mmHg)	134±18	135±19	127±18
Diastolic BP (mmHg)	78±11	76±10	78±10
Duration of diabetes (years)	NA	14 (6-21)	NA
Total Cholesterol (mg/dL)	187±45	176±46	176±39
HDL Cholesterol (mg/dL)	50±17	44±15	47±18
LDL Cholesterol (mg/dL)	112±42	101±39	106±44
Triglycerides (mg/dL)	152±80	153±92	144±74
Uric acid (mg/dL)	6.7±1.8	5.6±1.9	6.1±1.4
HbA1C	6.2±1.4	8.6±1.9	5.6±0.4
Allopurinol	42%	3.6%	NA
Renin angiotensin system inhibitors (%)	88%	64%	93%
Sympatholytic agents (%)	38%	28%	59%
Calcium antagonists (%)	42%	26%	40%
Diuretics (%)	52%	36%	41%

Data are summarized as mean ± standard deviation or as percent frequency, as appropriate. NA= not available
TABLE 1

FIG.3

Fixed effect model:
Pooled HR: 2.04, 95% CI: 1.11-3.75, P=0.02
Random effect model:
Pooled HR: 2.04, 95% CI: 1.11-3.75, P=0.02
Eterogeneity: I^2=0.01, Q-value=0.07 (d.f. 2), P=0.97

Hazard ratio and 95% CI

Forest plot of hazard ratios for cardiovascular events (GT/TT versus GG genotypes) in the three study cohorts. For the calculation of the typical effect, both fixed and random effects models were applied. Data are hazard ratios, 95% CIs and P values. Heterogeneity was also reported in terms of I^2, Q-value (and degree of freedom, d.f.) and P value.

CONCLUSIONS

In a meta-analysis of three cohorts formed by patients at high cardiovascular risk, the T allele of the rs734553 polymorphism of the GLUT9 gene predicts a doubling in the risk for incident cardiovascular events. This meta-analysis is coherent with previous studies linking the same polymorphism with the risk of kidney failure, hypertension and atherosclerosis. Findings in this study supports the hypothesis of a causal role of hyperuricemia in cardiovascular disease in high risk conditions.