Congresso Nazionale SIGG

Firenze, 29 novembre 2007

Farmacogenetica delle rezioni avverse

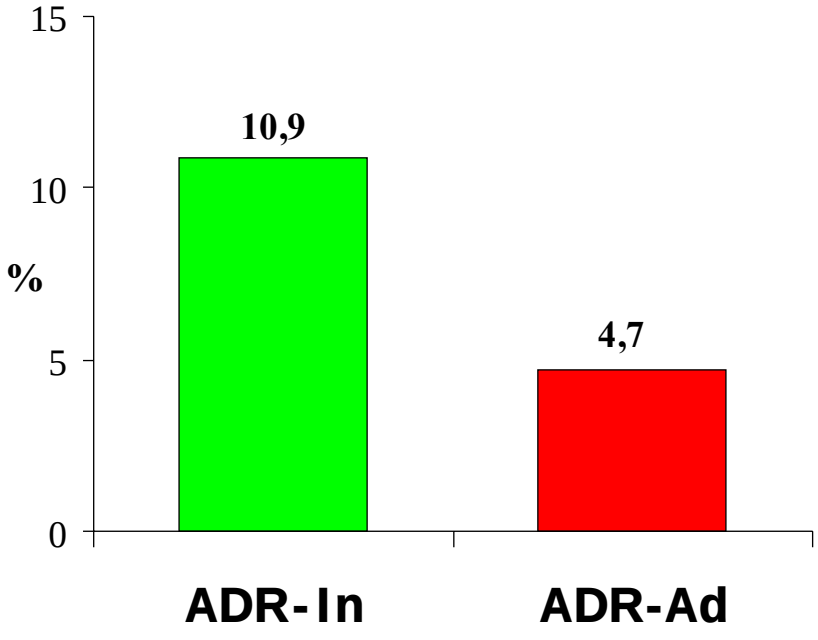
Alberto Pilotto

Department of Medical Sciences
Geriatric Unit & Gerontology-Geriatrics Research Laboratories
Casa Sollievo della Sofferenza, IRCCS
San Giovanni Rotondo, Italy

Incidenza di ADR in pazienti ospedalizzati: meta-analisi di 39 studi prospettici negli USA, 1966-1996

62.480 pazienti: Prevalenza ADR severe=6.7%, ADR fatali=0.32%

≈ 6.7% ≈



ADR-In
ADR avvenute in pazienti mentre erano ricoverati in ospedale

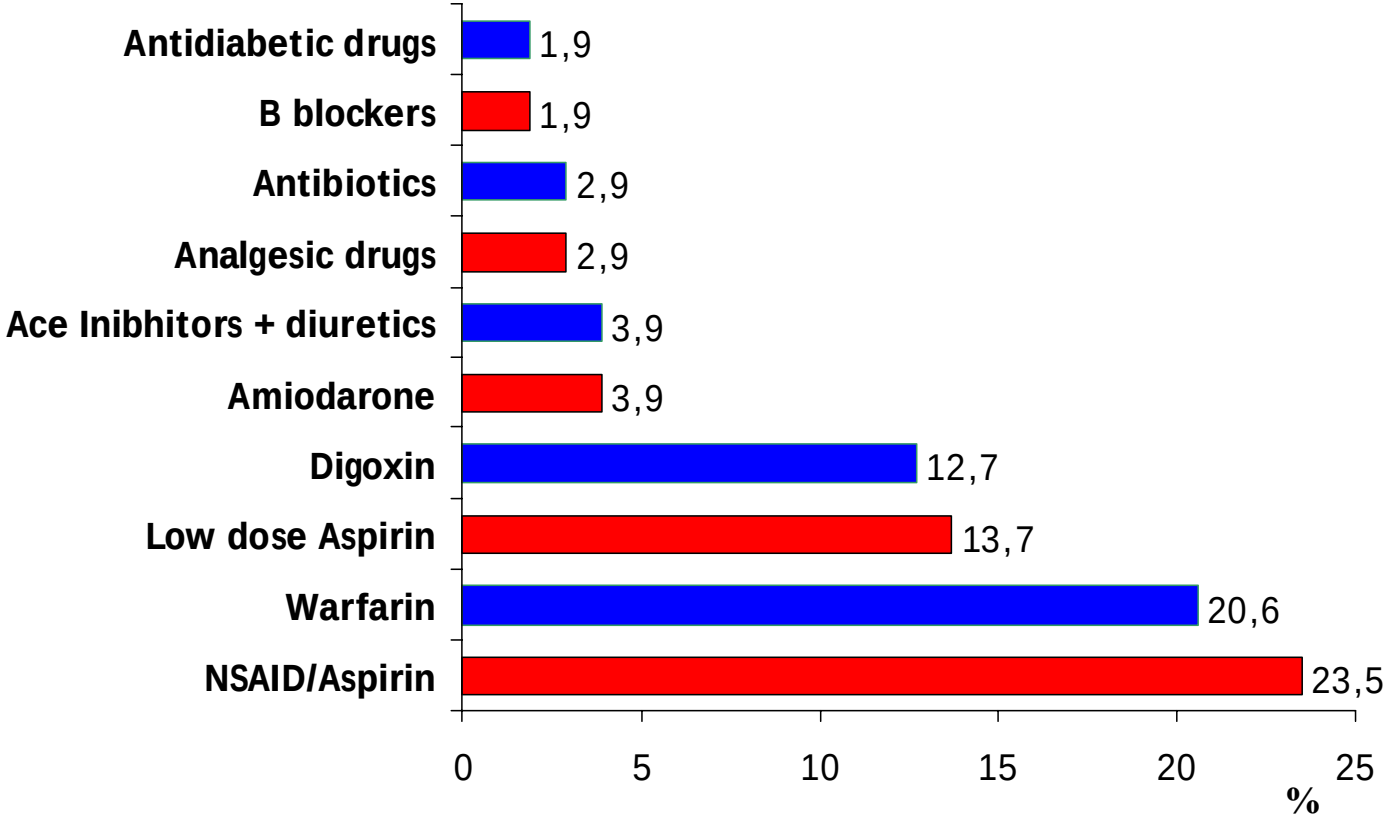
ADR-Ad
ADR che hanno indotto ricovero in ospedale

Lazarou, JAMA 1998; 279:1200-5

Farmaci responsabili di ADR severa

1756 patients, admitted to Geriatric Unit (Nov. 2004-Dec.2005)

ADR = 102 cases (5.8%) of all admissions



Franceschi, Drug Saf 2007, in press

Pharmacogenetics

Polymorphisms in the genes that code for drug-metabolising enzymes, drug transporters, drug receptors can affect:

- efficacy

- interactions with other drugs

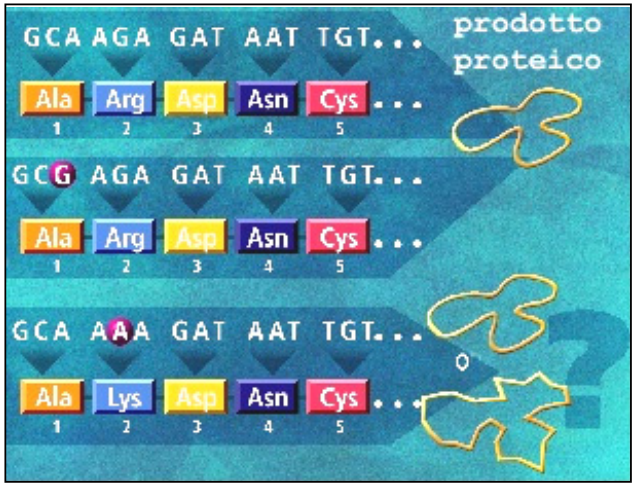
- adverse drug reactions

It is likely to be among the first clinical applications of the Human Genome Project

Ginsburg, Arch Intern Med 2005; 165: 2331-6

Mutazioni genetiche

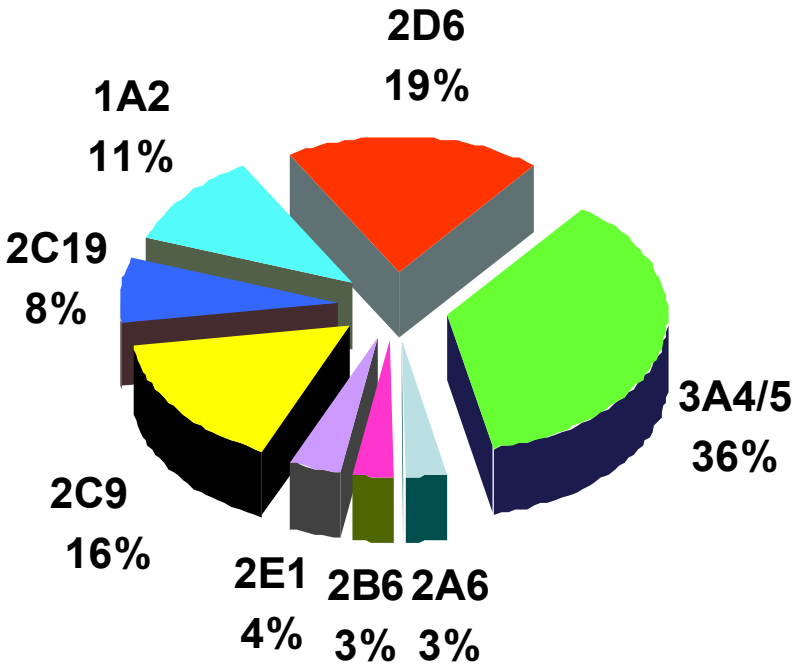
Rare, presenti < 1% della popolazione, recenti dal punto di vista evolutivo, modifiche fenotipiche rilevanti (malattie mendeliane)



Comuni, presenti > 1% della popolazione, antiche dal punto di vista evolutivo, piccole variazioni fenotipiche, mediano con i fattori ambientali (fattori di rischio), polimorfismi

Dallapiccola B et al, 2006

Cytochrome P 450 System and drug metabolism



Genotyping as a tool to predict ADRs

More than 80% of human drug oxydation is due to six CYP isoenzymes:

3A4/5

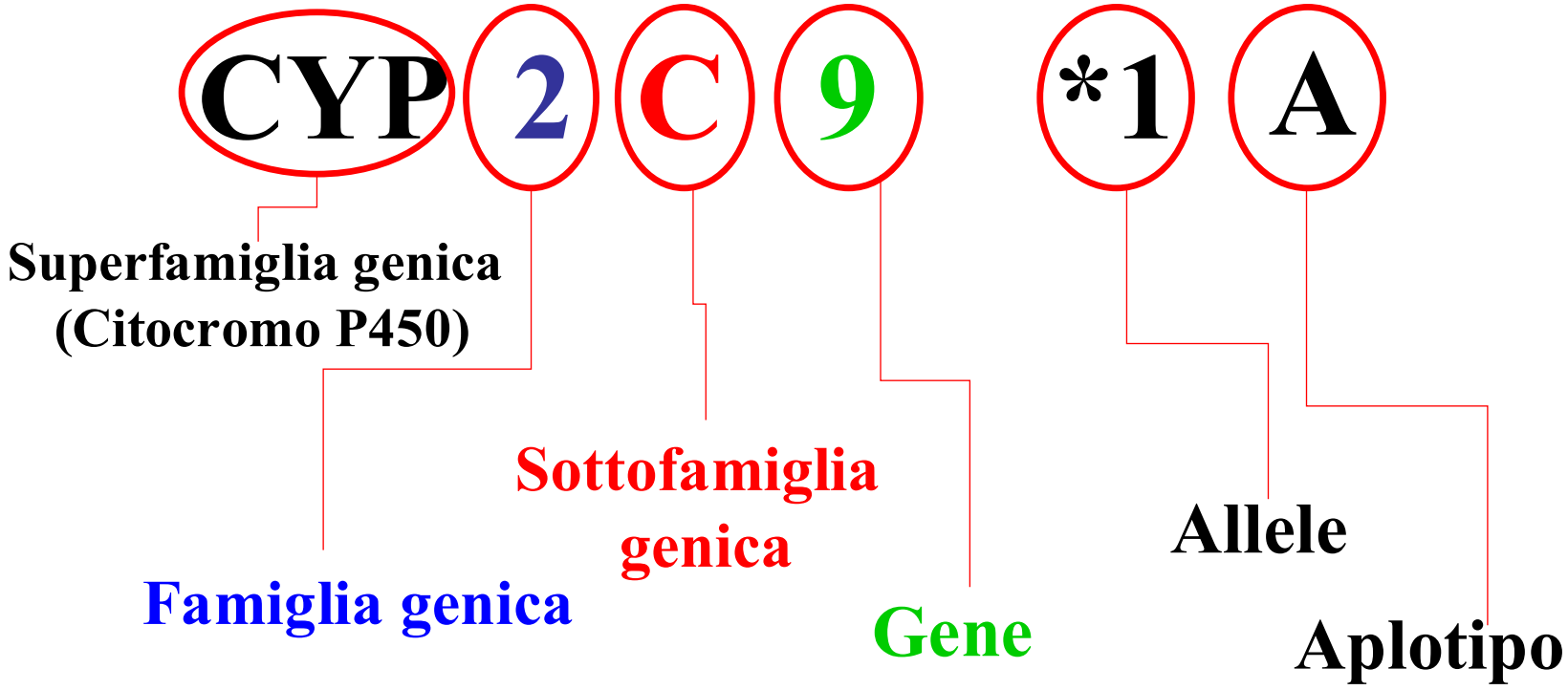
2D6

2C19

2C9

Guzey, Curr Top Med Chem 2004; 4:1411-21

Nomenclatura del sistema del Citocromo P450



Home page of the Human Cytochrome P450 (CYP) Allele Nomenclature Committee (http://www:cypalleles.ki.se)

Drugs that are substrates for CYP 3A4

SUBSTRATI 3A4

Ca++ Antagonisti
diltiazem, **felodipina,**
nifedipina, verapamile

Benzodiazepine
alprazolam, midazolam,
triazolam

Statine
atorvastatina, lovastatina

Antibiotici macrolidi
eritromicina,
claritromicina

Agenti anti-HIV
Indinavir, ritonavir,
saquinavir

INIBITORI

FORTI
Agenti anti-HIV
Claritromicina
Ketoconazolo

MODERATI
Fluconazolo
Verapamile
Succo di pompelmo

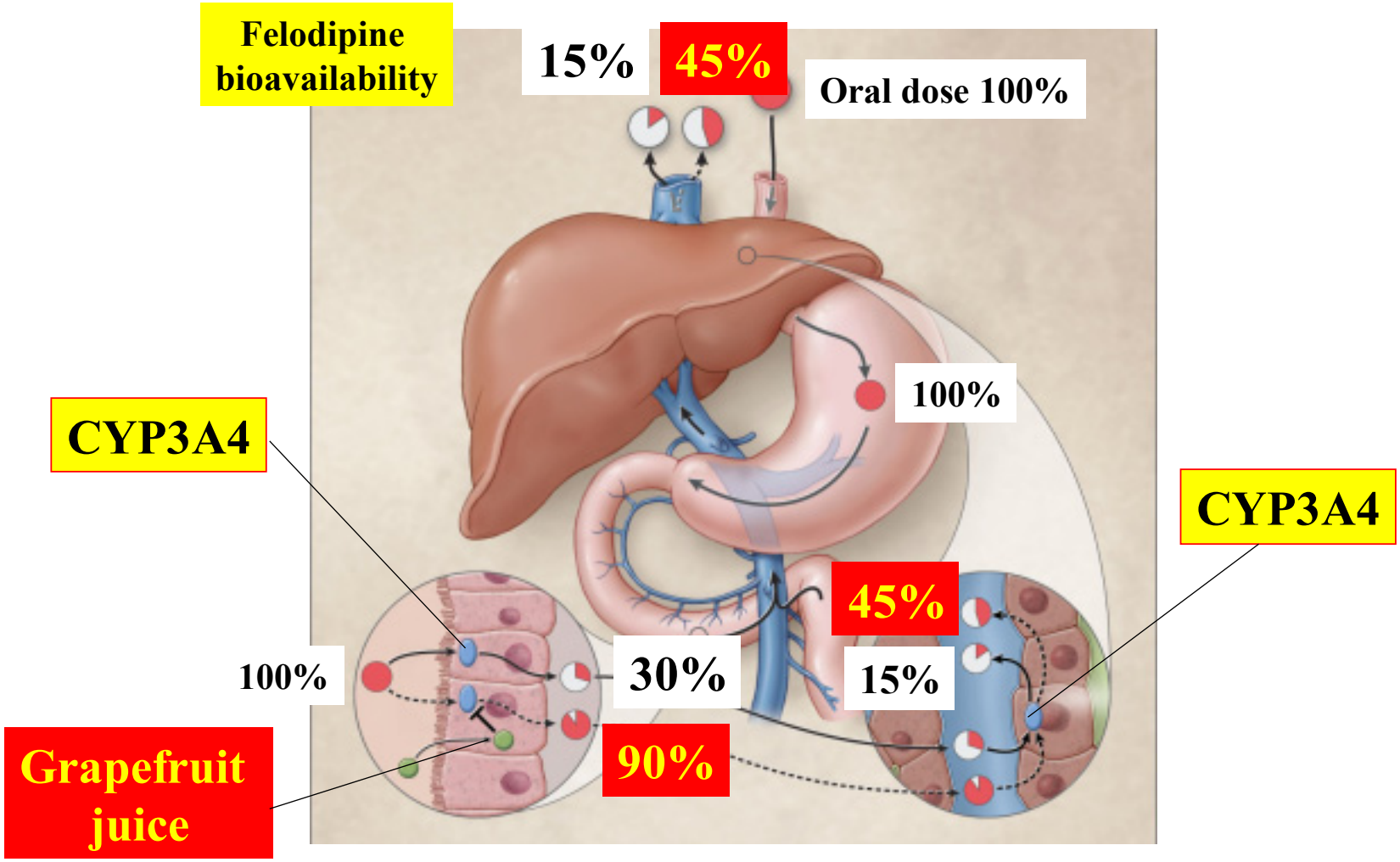
LIEVI
cimetidina

INDUTTORI

Fenobarbital
Carbamazepina
Oxcarbamazepina
Glicorticoidi
Rifampicina
Rifabutina
Troglitazone

http://medicine.iupui.edu/flockhart/table/htm 2007

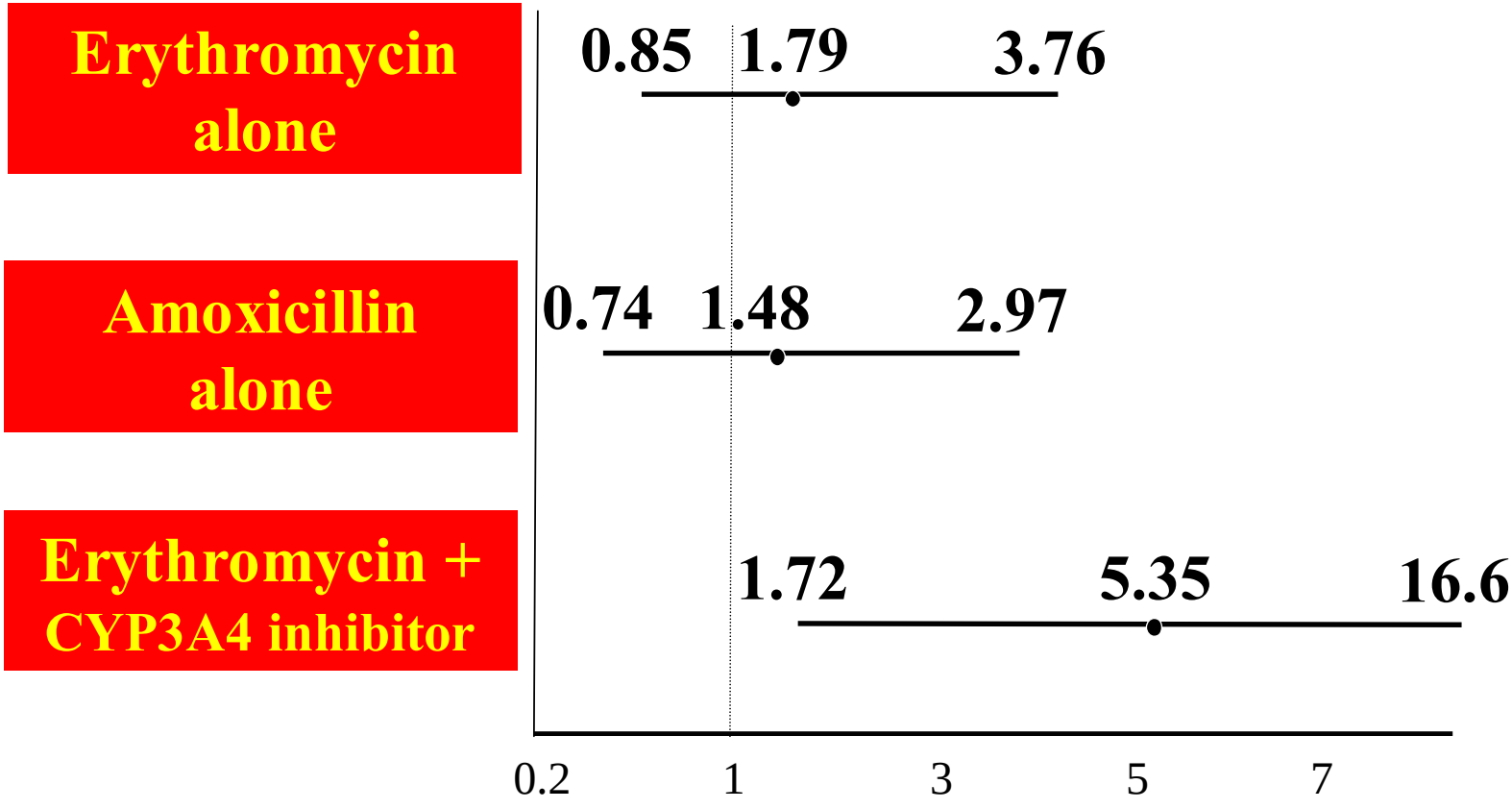
Metabolism after Oral administration of Felodipine and its interaction with CYP3A4 Inhibitors



Wilkinson, NEJM 2005; 352: 2211-21

Risk of sudden death from cardiac causes according to use of CYP3A4 inhibitors and antibiotics (1476 cases)

CYP3A4 INHIBITORS: nitroimidazole antifungal agents, diltiazem, verapamil, troleandomycin



Ray, NEJM 2004; 351: 1089-96

Drugs that are substrates for CYP 2D6

Beta-bloccanti:
Carvedilolo, Metoprololo, propanololo, Timololo

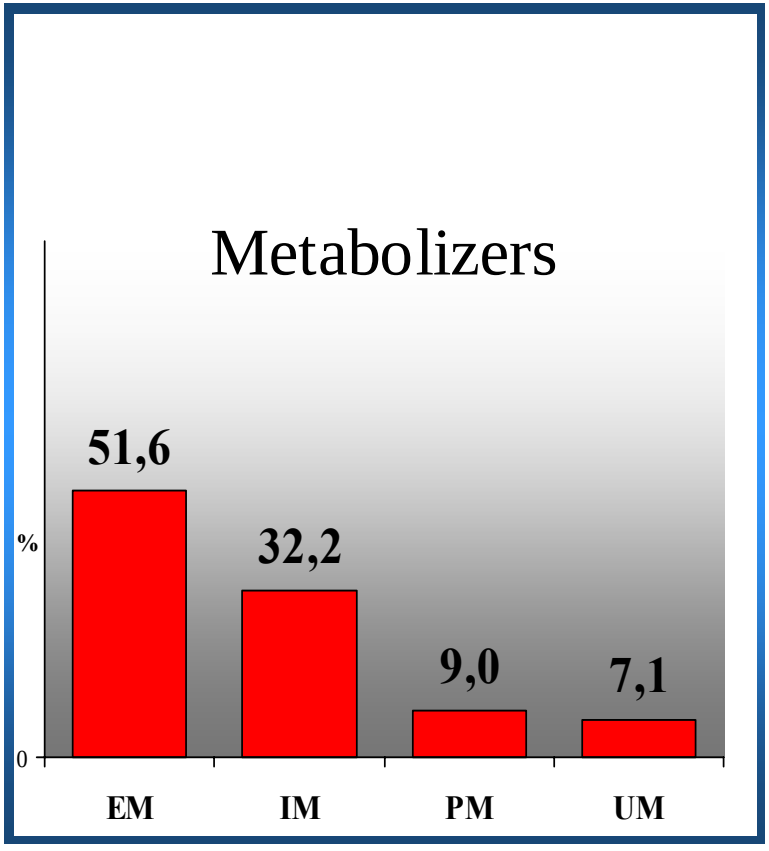
Antidressivi:
Fluoxetine, Fluvoxamine, Imipramine Paroxetina

Antipsicotici:
Aloperidolo, Risperidone

Oppioidi:
Codeina, oxicodone

Antiaritmici:
Flecainide, Mexiletina, Propafenone

CYP 2D6

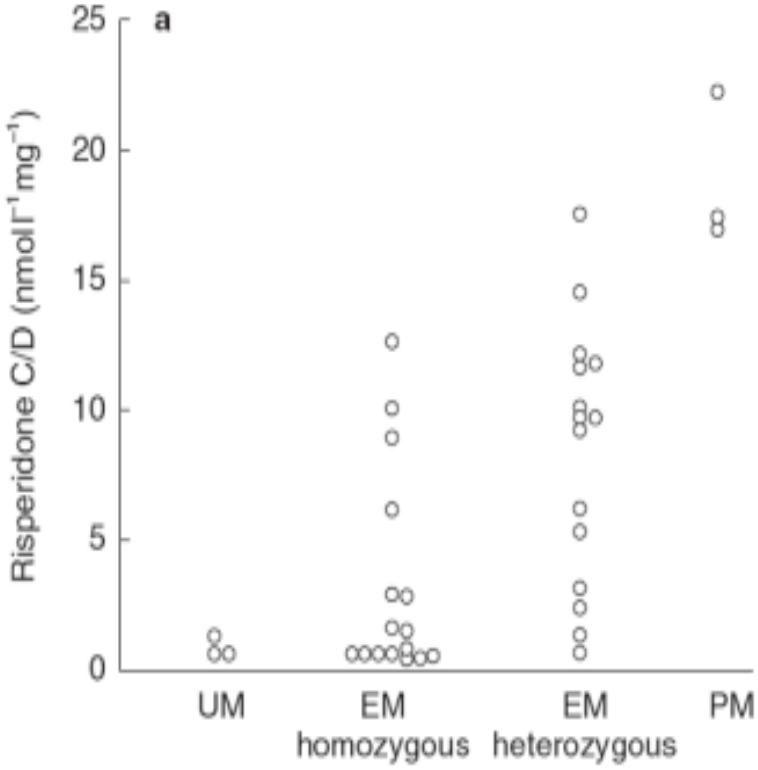


Cacabelos, Curr Alzheimer Res 2007;4:479-500

Molecolar genetics of CYP 2D6: clinical relevance

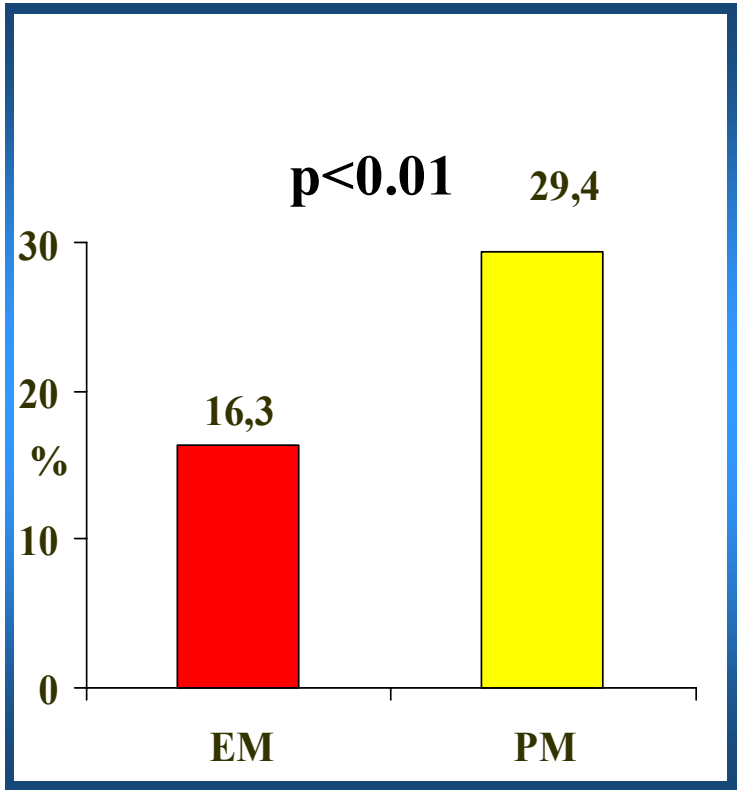
CYP 2D6 genotype and plasma concentration of psychotropic drugs

RISPERIDONE



Scordo, Psychopharmacology 1999; 147:300-5

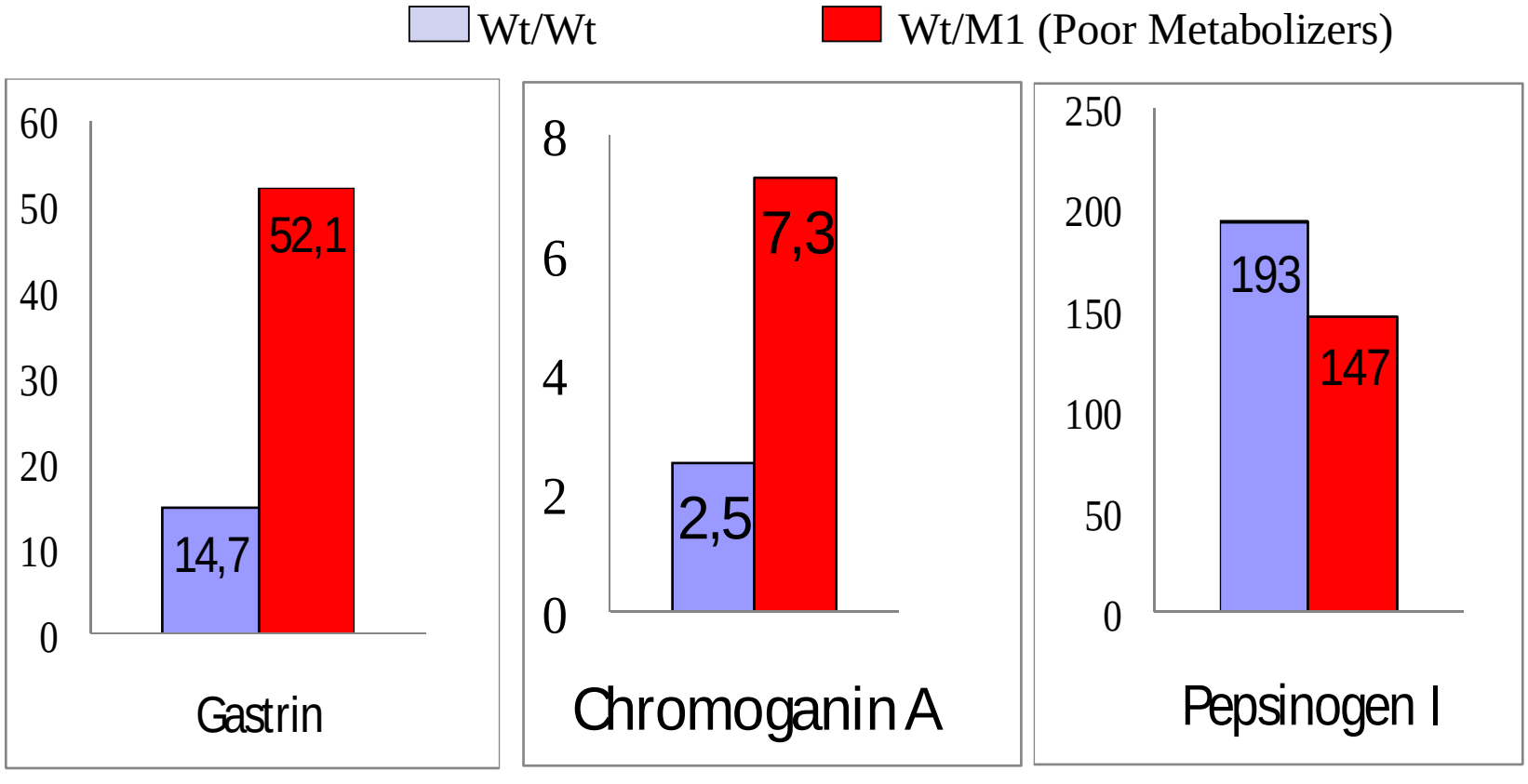
HALOPERIDOL



Bertilsson, Br J Clin Pharmacol 2002; 53:111-22

CYP 2C19 polymorphisms and PPI: effects of on gastrin, PG I, and chromogranin A

72 patients on long-term treatment (>1 year) with omeprazole 20 mg daily

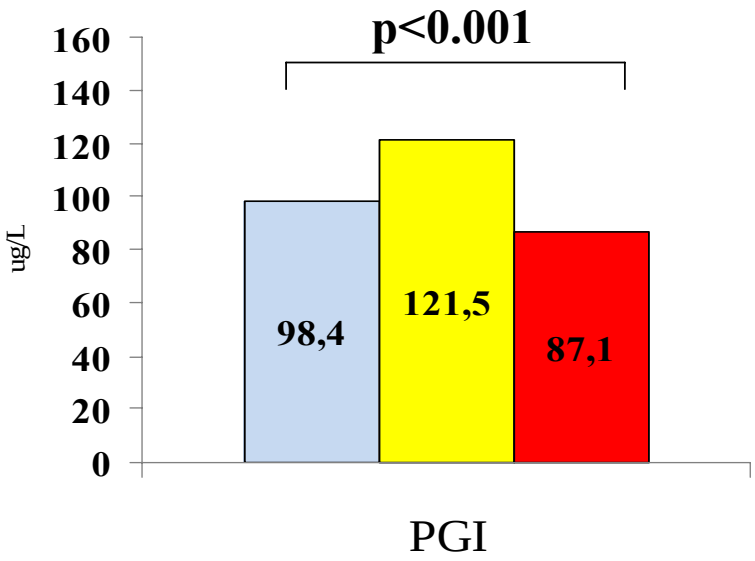


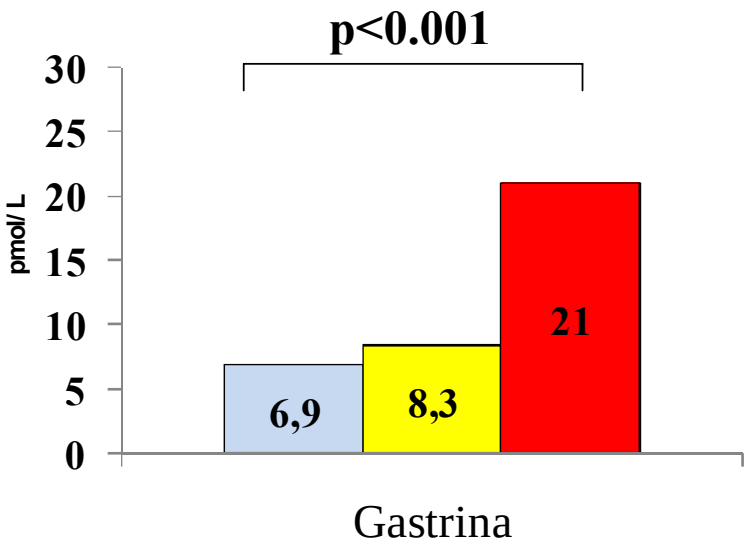
Sagar, Aliment Pharmacol Ther 2000;14:1495-502

Clinical usefulness of serum pepsinogens I and II, gastrin-17 and anti-Helicobacter pylori antibodies in the management of dyspeptic patients in primary care

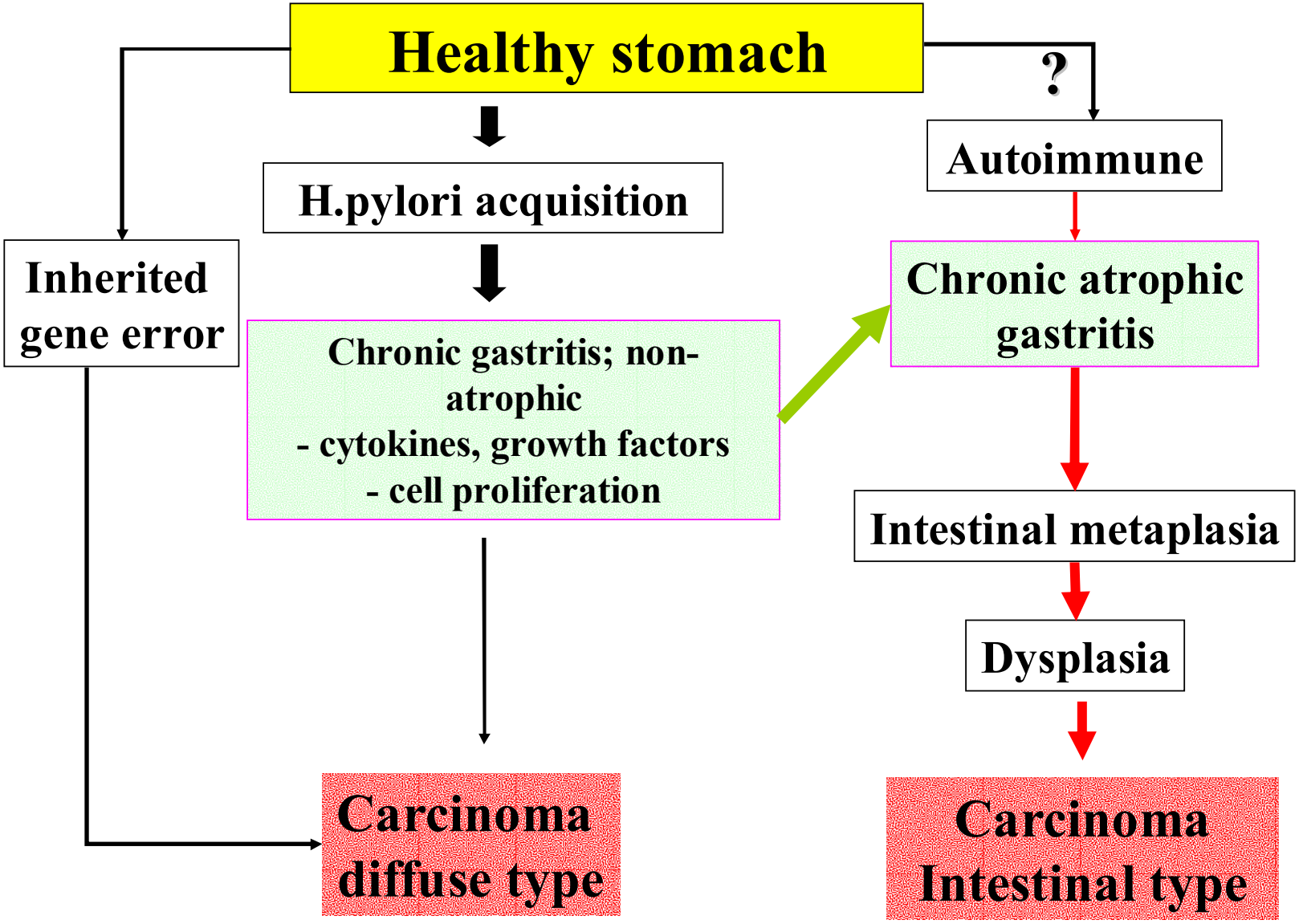
362 patients with dyspeptic symptoms
F=208, M=154, mean age=50.6 ± 16 years, range=18-88 years

Normal (n=138) Non-atrophic chronic gastritis (n=89) Atrophic chronic gastritis (n=60)





Germanà, Dig Liver Dis 2005;37:501–8



Sipponen, APT 1998,12 (Suppl 1):61-71

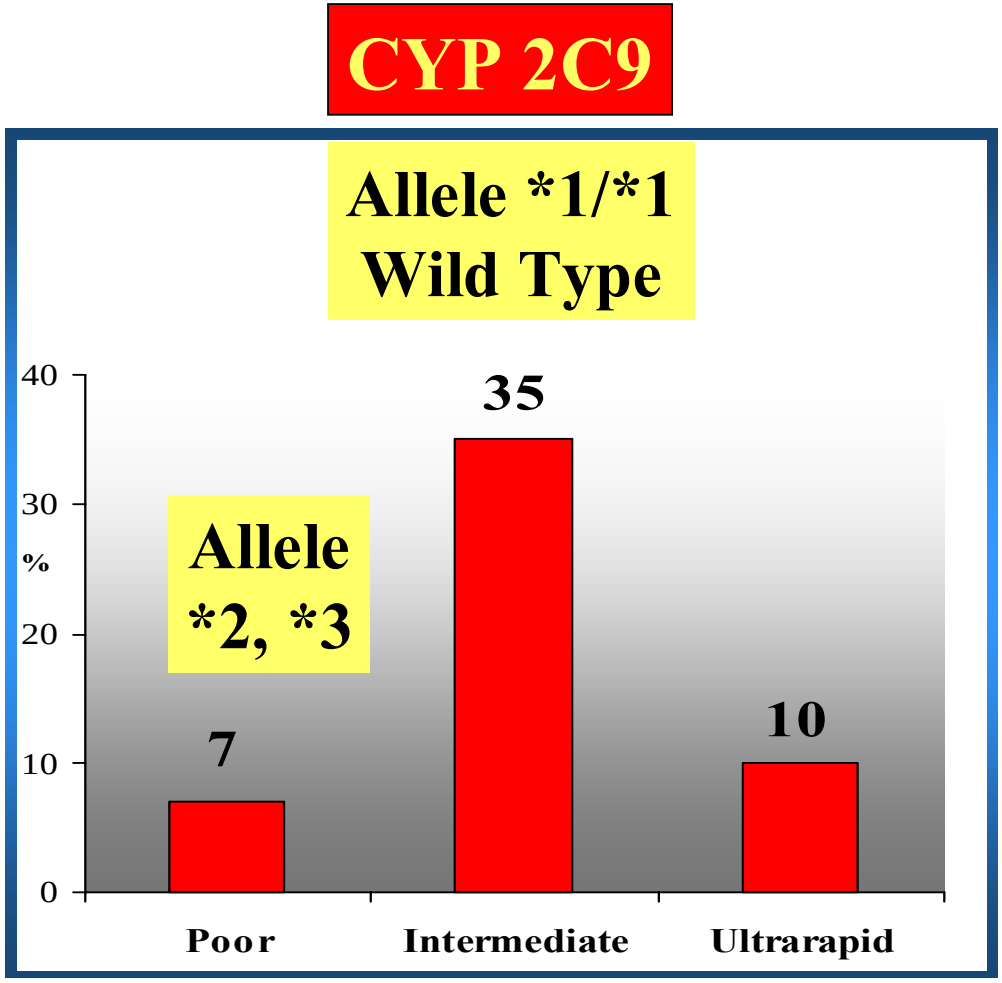
Drugs that are substrates for CYP 2C9

Celecoxib

Diclofenac
Naproxen
Nimesulide
Piroxicam

Tolbutamide
Glipizide

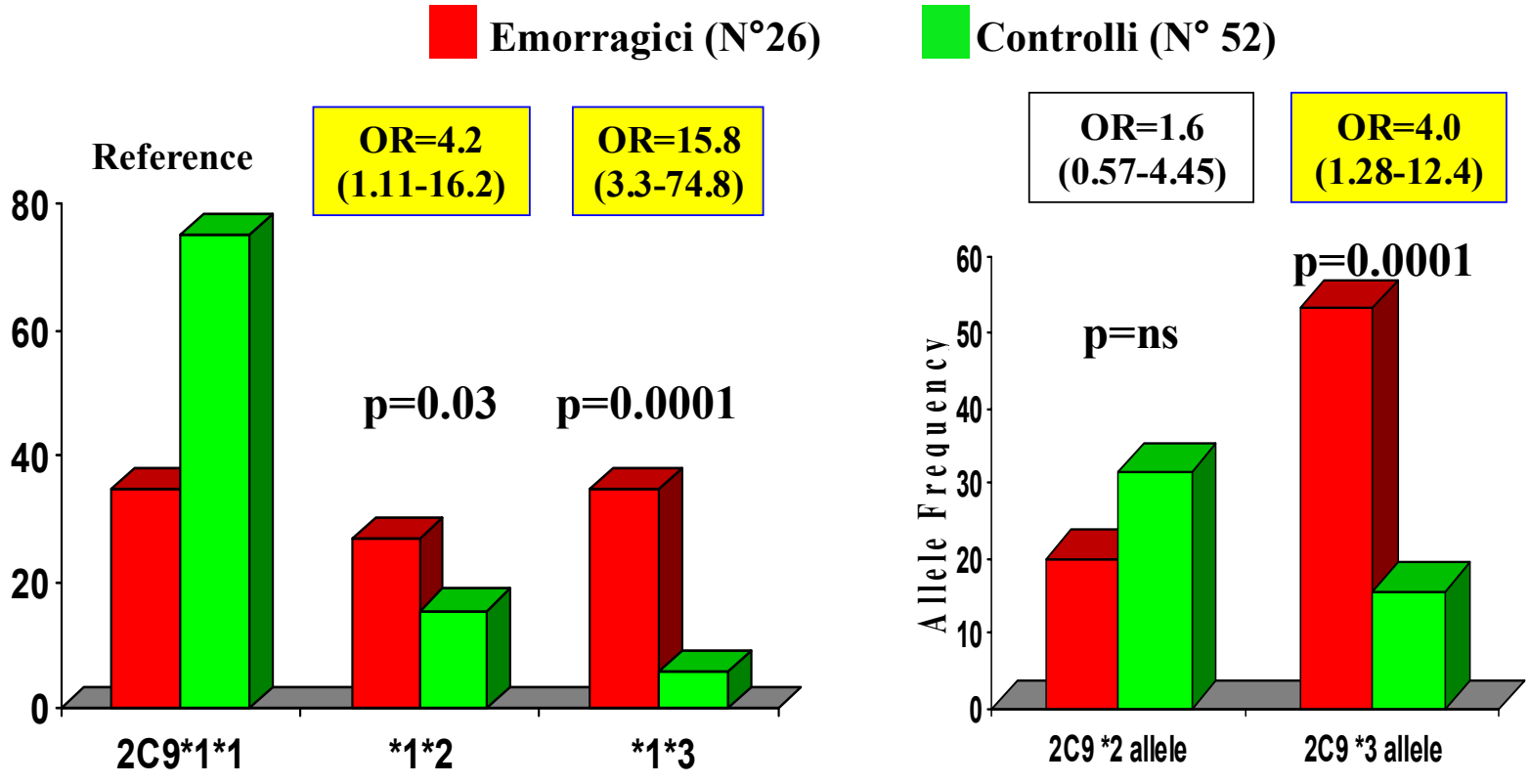
Warfarin



Lee, Pharmacogenetics 2002; 12:251-63

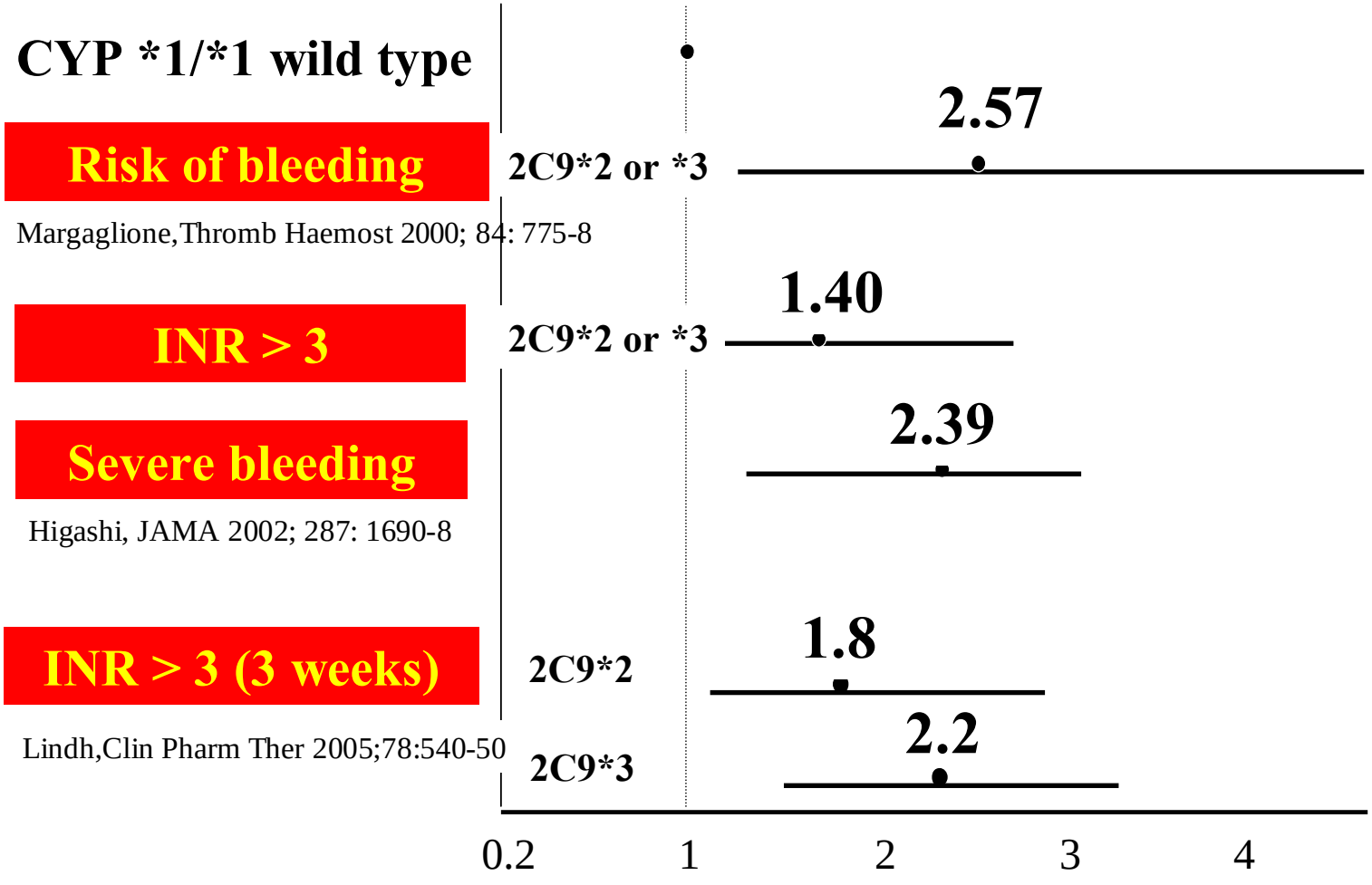
Rischio di emorragia gastroduodenale da FANS: ruolo dei polimorfismi genetici del Citocromo P450 2C9

Farmaci: celecoxib, diclofenac, nimesulide, naproxene, piroxicam < 30 giorni
H pylori negativi, no gastroprotezione



Pilotto et al, Gastroenterology 2007; 133: 465-71

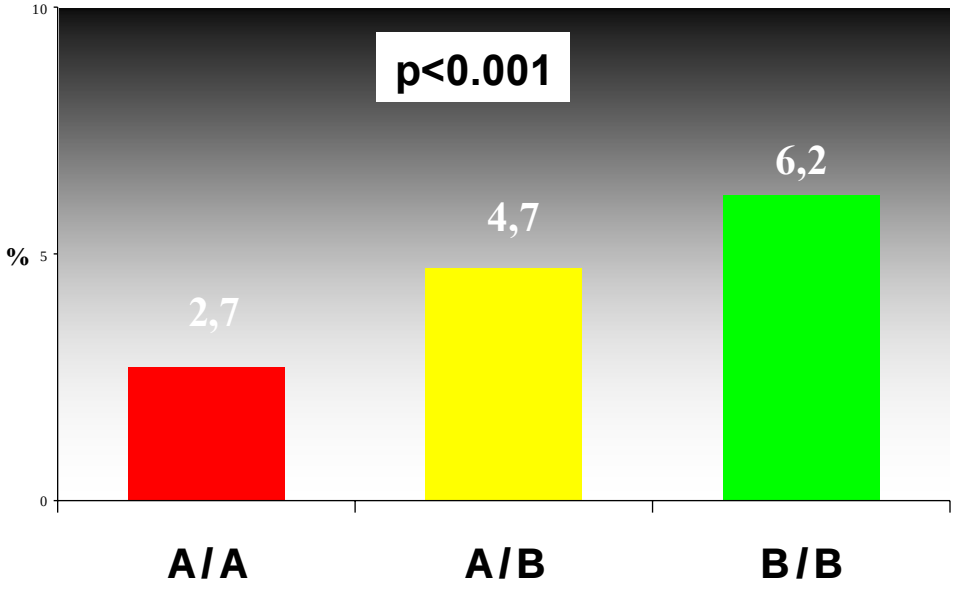
Association between CYP2C9 genetic variants and anticoagulation-related outcomes



Vitamin K Oxide Reductase Complex 1 (VKORC1) polymorhisms and warfarin dose

Retrospective study in European-American patients in long-term maintenance treatment with warfarin

Maintenance dose of warfarin (mg daily)



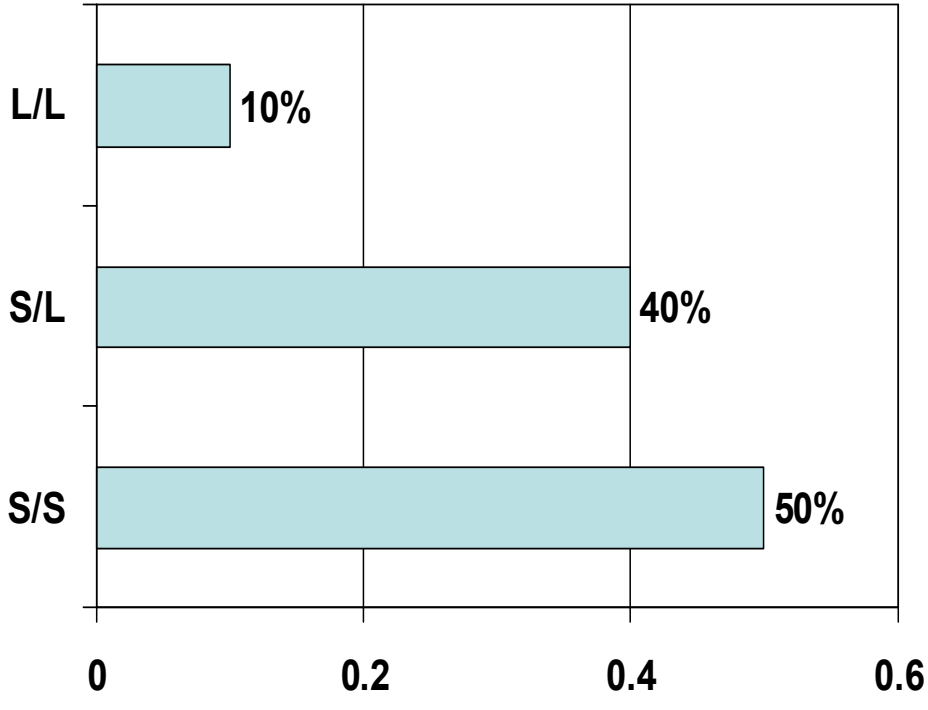
A = low-dose haplotype group

B= high-dose haplotype group

Rieder, NEJM 2005;352: 2285-93

Serotonin Transporter Gene-Linked Polymorphic Region (HTTLPR) and antidepressant ADRs

109 patients treated with:
mirtazapine (65), citalopram (10), escitalopram (7), venlafaxine (6), paroxetine (5), doxepin (5), other antidepressants (11)



HTTLPR S/S homozygotes and S/L heterozygotes suffered more of antidepressant-associated ADRs (p=0.002)

Popp, Pharmacogenomics 2006; 7: 159-66

Farmacogenetica Citocromo-P450 indipendente

N-acetiltransferasi (NAT2)	Sulfamidici, isoniazide, idralazina
UDP glucoronisiltransferasi (UGT1A1)	Irinotecan
Tiopurina metiltransferasi (TPMT)	Azatioprina, 6-mercaptopurina
Diidropirimidina deidrogenasi (DPD)	5-fluorouracile
Metilenetetraidrofolato reduttasi (MTHFR)	Metotrexate

Mladosievicova, Neoplasma 2007;54:181-8

Criteri di Evitabilità di ADR (Hallas)

1756 patients, admitted to Geriatric Unit (Nov. 2004-Dec.2005)

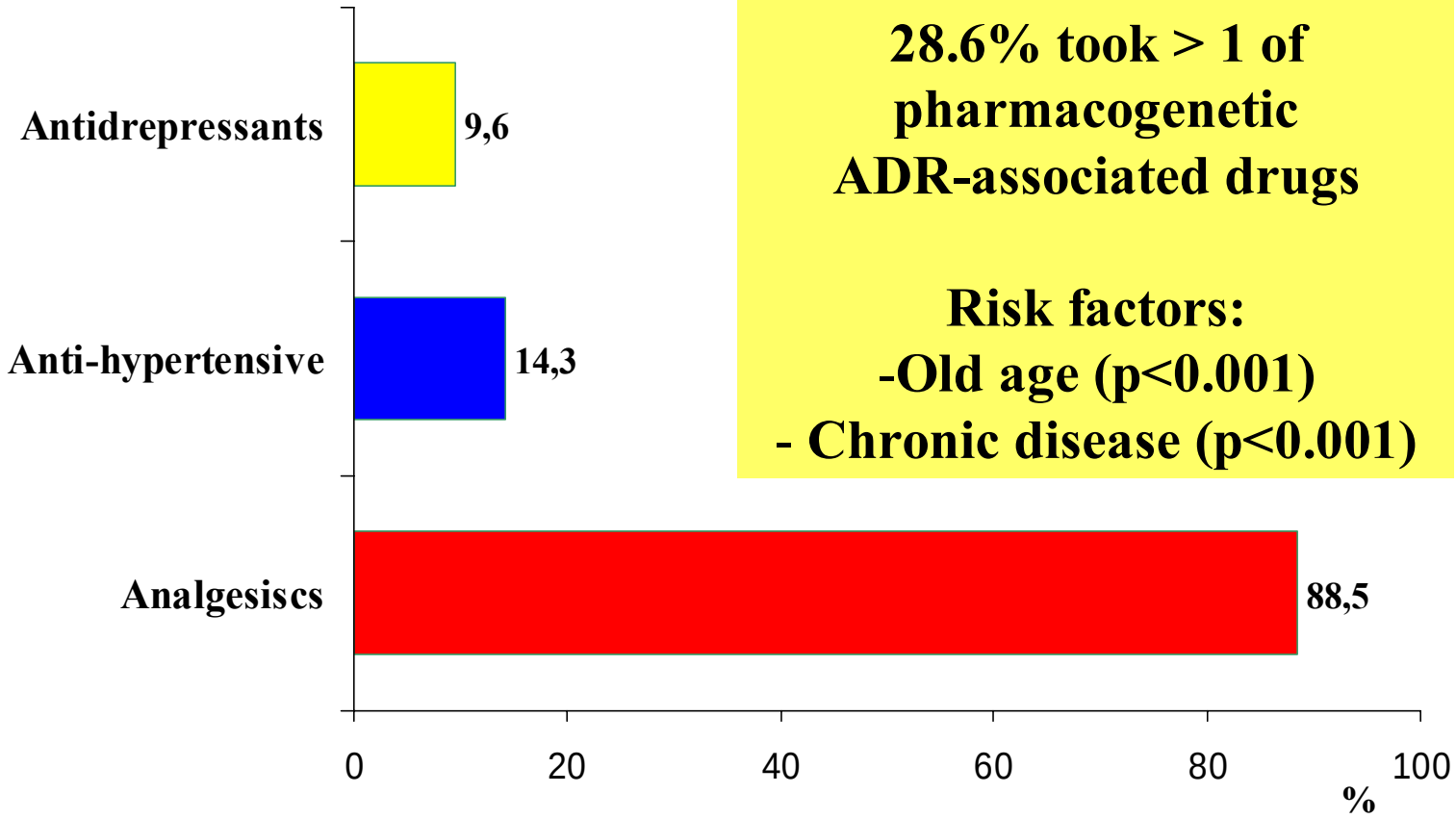
ADR = 102 cases (5.8%) of all admissions

	Definitely avoidable		Possible avoidable
	17 (16.5%)	29 (28.4%)	32 (31.4%)
	Inappropriate prescription	*No gastroprotection*	*Inadequate monitoring*
NSAID/ASA	5 (29.4%)	29 (100%)	1 (3.1%)
Warfarin	3 (17.6%)	-	13 (40.6%)
Digoxin	1 (5.9%)	-	12 (37.5%)
Antidiabetics	-	-	2 (6.3%)
Amiodarone	1 (5.9%)	-	1 (3.1%)
Antihypertensive	4 (23.5%)	-	3 (9.4%)
Neurological	3 (17.6%)	-	-

Franceschi, Drug Saf 2007, in press

Defining the opportunity for pharmacogenetic intervention in primary care

607 patients in primary care (USA), 16 drugs cause ADRs



28.6% took > 1 of pharmacogenetic ADR-associated drugs

Risk factors:
-Old age (p<0.001)
- Chronic disease (p<0.001)

Grice, Pharmacogenomics 2006; 7: 61-5

Grazie per l'attenzione

Donato Antonacci, MD
Leandro Cascavilla, MD
Michele Corritore, MD
Piero D'Ambrosio, MD
Maria Grazia Longo, MD
Valeria Niro, MD
Francesco Paris, MD
Giuseppe Rinaldi, MD
Carlo Scarcelli, MD
Margherita Zurro, MD

Marilisa Franceschi, MD
Filomena Addante, MD
Giuliana Placentino, Psicol.
Grazia D'Onofrio, Psicol.
Anna Maria Pazienza, Stat.

Davide Seripa, BD
M.Giovanna Matera, BD
Veronica Goffredo, BD
Carolina Gravina, Tec. Lab.
Maria Urbano, Tec. Lab.