Valutazione della calcifilassi coronarica **I**n pazienti a medio-elevato rischio cardiovascolare sottoposti a TC coro**N**arica in terapia anticoagulante orale per fibrillazione atriale non valvolare: V**K**A vs DO**A**Cs

Dasseni N.

Cattedra ed U.O. Cardiologia Spedali Civili, Brescia

VINKA TRIAL

GIORNATE CARDIOLOGICHE TORINESI

PRiME PRevention in Medical Experiences

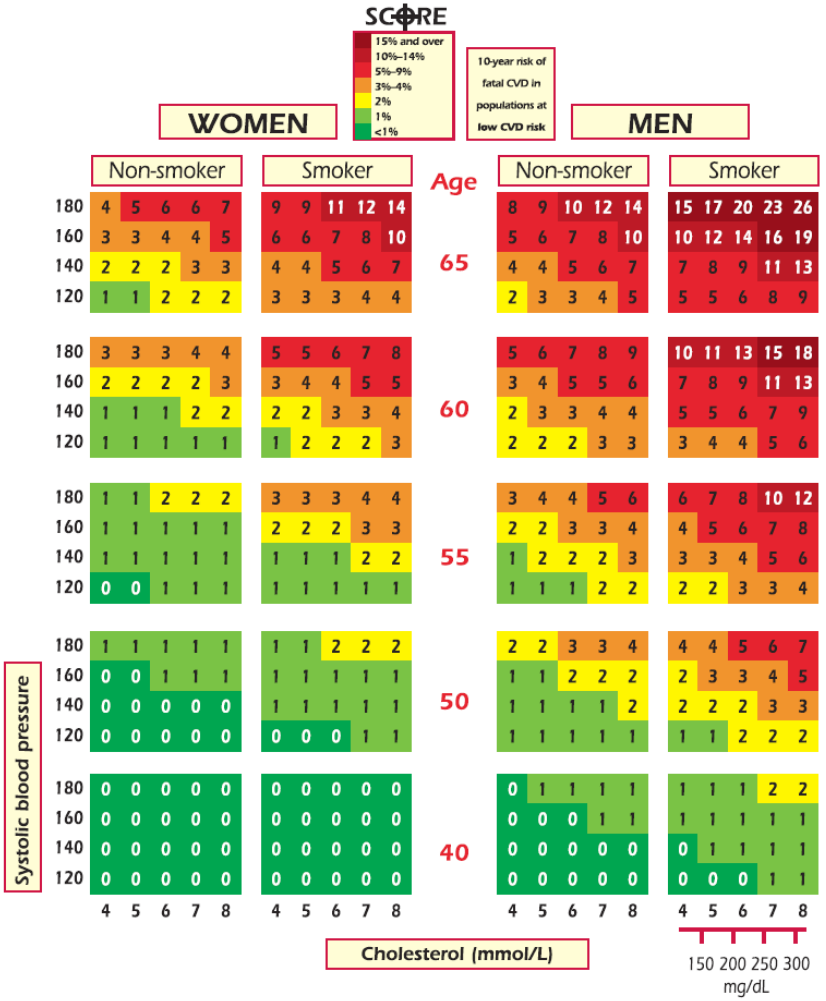
2016 European Guidelines on cardiovascular disease prevention in clinical practice

The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)

How?

Recommendation for how to estimate cardiovascular risk

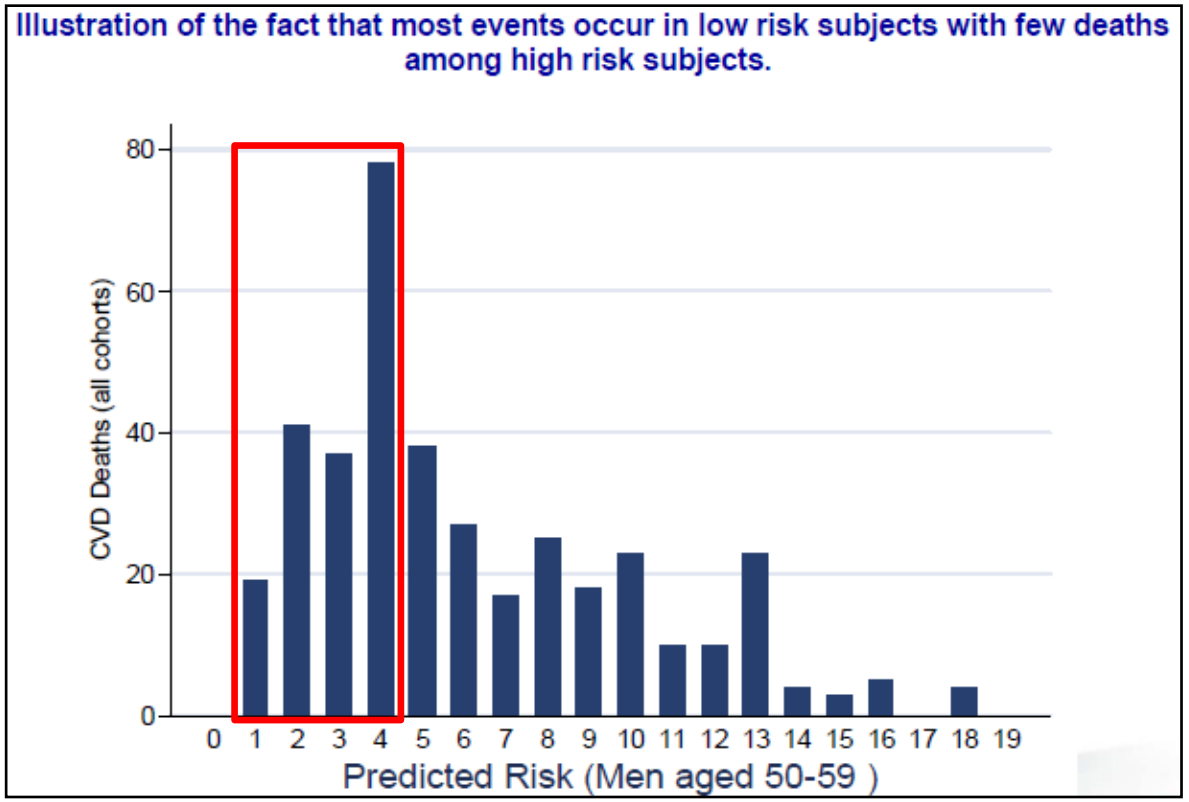
Recommendation	Class[a]	Level[b]	Ref[c]
Total CV risk estimation, using a risk estimation system such as SCORE, is recommended for adults >40 years of age, unless they are automatically categorised as being at *high-risk* or *very high-risk* based on documented CVD, DM (>40 years of age), kidney disease or highly elevated single risk factor (Table 5).	I	C	11, 25



European Heart Journal (2016) 37, 2315–2381

Very high-risk	Subjects with any of the following: • Documented CVD, clinical or unequivocal on imaging. Documented clinical CVD includes previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm and PAD. Unequivocally documented CVD on imaging includes significant plaque on coronary angiography or carotid ultrasound. It does NOT include some increase in continuous imaging parameters such as intima–media thickness of the carotid artery. • DM with target organ damage such as proteinuria or with a major risk factor such as smoking or marked hypercholesterolaemia or marked hypertension. • Severe CKD (GFR <30 mL/min/1.73 m2). • A calculated SCORE ≥10%.
High-risk	Subjects with: • Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg. • Most other people with DM (with the exception of young people with type 1 DM and without major risk factors that may be at low or moderate risk). • Moderate CKD (GFR 30–59 mL/min/1.73 m²). • A calculated SCORE ≥5% and <10%.

Moderate-risk	SCORE is ≥1% and <5% at 10 years. Many middle-aged subjects belong to this category.
Low-risk	SCORE <1%.



Graham et al. EJCVPrev 2007;14:E1-E40

Table 3 Advantages and limitations in using the SCORE risk charts

Advantages

- Intuitive, easy to use tool.
- Establishes a common language of risk for healthcare professionals.
- Allows a more objective assessment of risk.
- Takes account of the multifactorial nature of CVD.
- Allows flexibility in management; if an ideal risk factor level cannot be achieved, total risk can still be reduced by reducing other risk factors.
- Deals with the problem of a low absolute risk in young people with multiple risk factors: the relative risk chart helps to illustrate how a young person with a low absolute risk may be at a substantially high and reducible relative risk; calculation of an individual's "risk age" may also be of use in this situation.

Limitations

- Estimates risk of fatal but not total (fatal + non-fatal) CV risk for reasons outlined in text.
- Adapted to suit different European populations, but not different ethnic groups within these populations.
- Limited to the major determinants of risk.
- Other systems have more functionality, although applicability to multiple countries is uncertain.
- Limited age range (40–65 years).

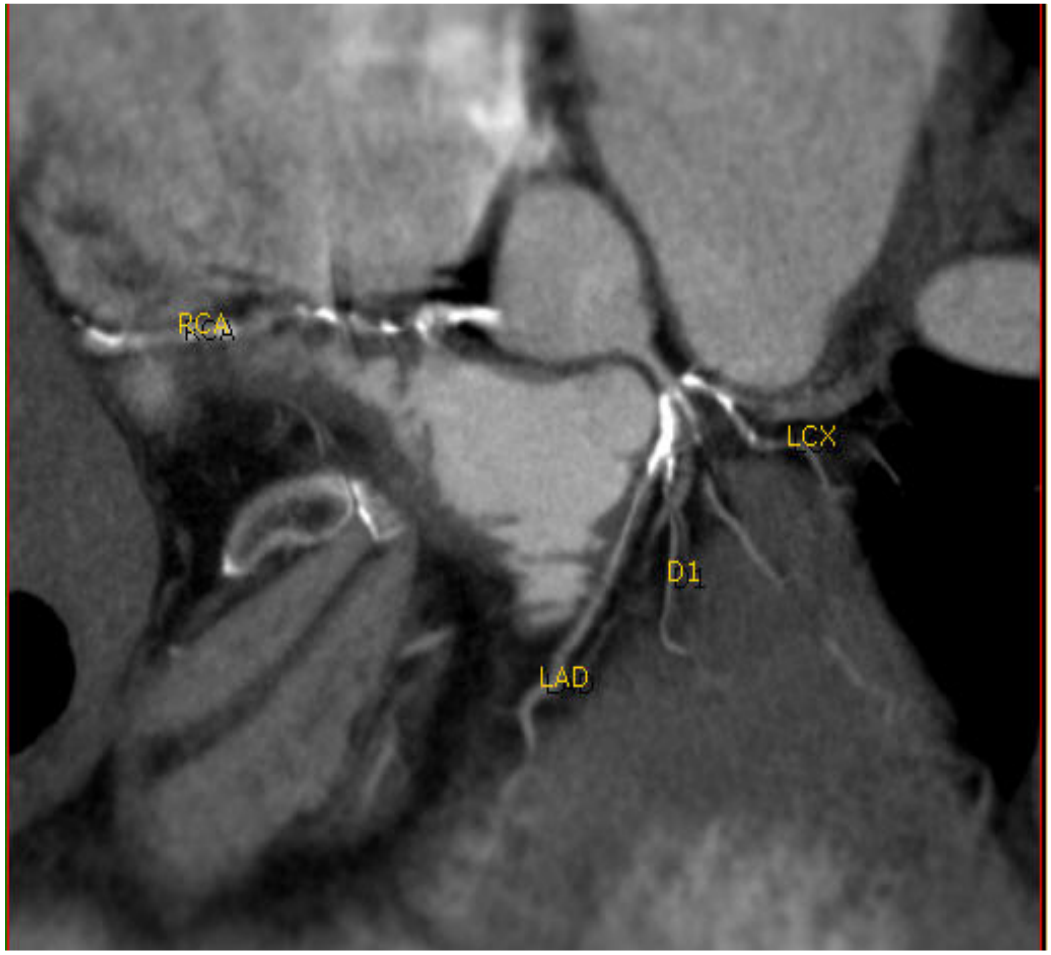
Table 4 Examples of risk modifiers that are likely to have reclassification potential (see following sections for details)

Socio-economic status, social isolation, or lack of social support.
Family history of premature CVD.
BMI and central obesity.
CT coronary calcium score.
Atherosclerotic plaques determined by carotid artery scanning.
ABI.

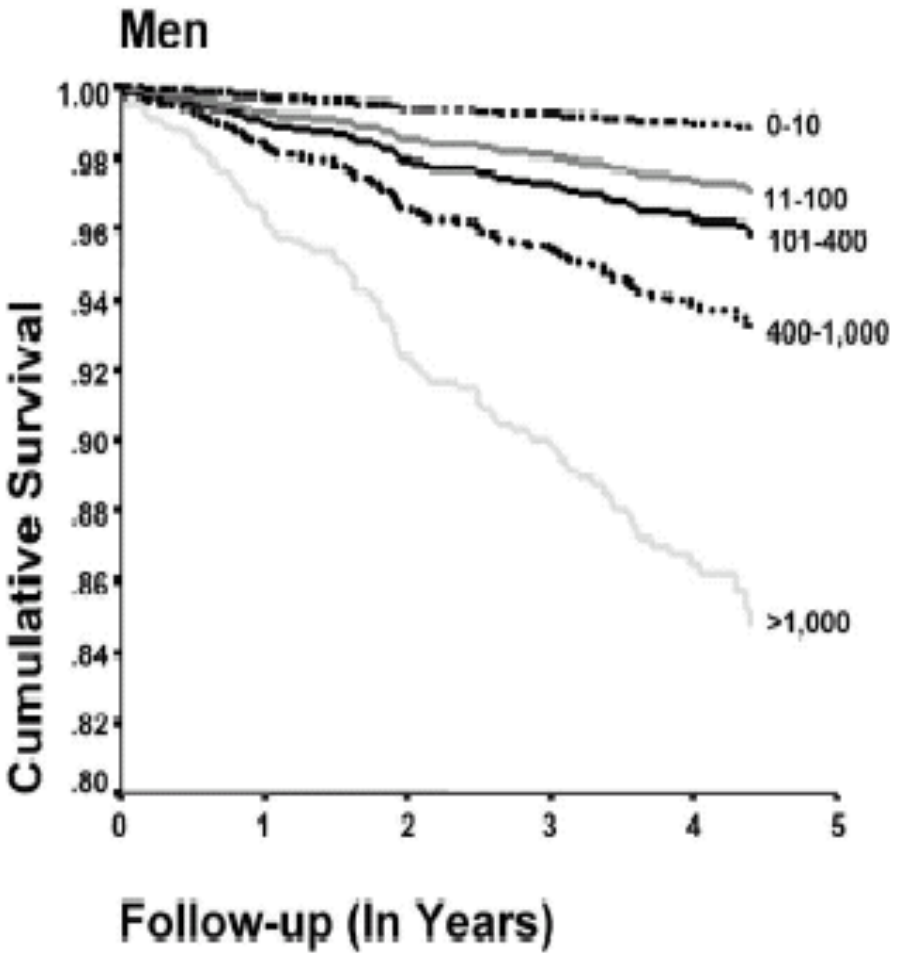
European Heart Journal (2016) 37, 2315–2381

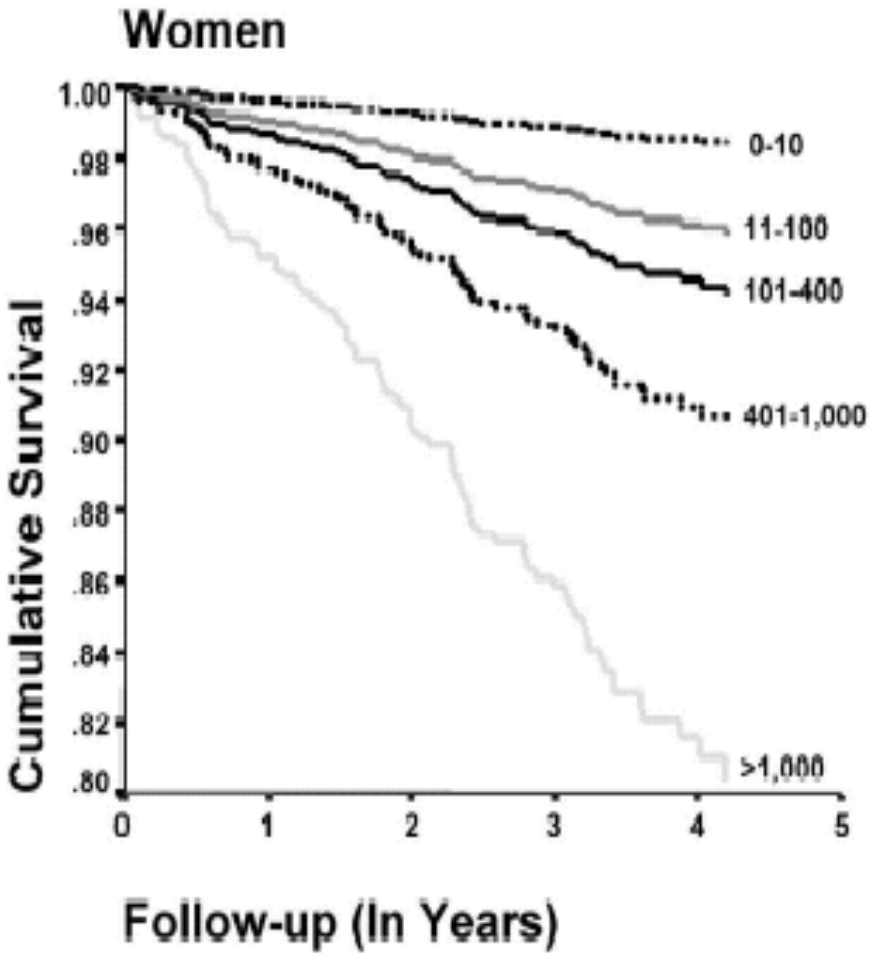
Coronary Calcium Score

La rilevazione della calcificazione delle arterie coronarie mediante TC e la sua espressione quantitativa con il relativo score sembra essere un importante fattore predittivo della malattia e degli eventi aterosclerotici



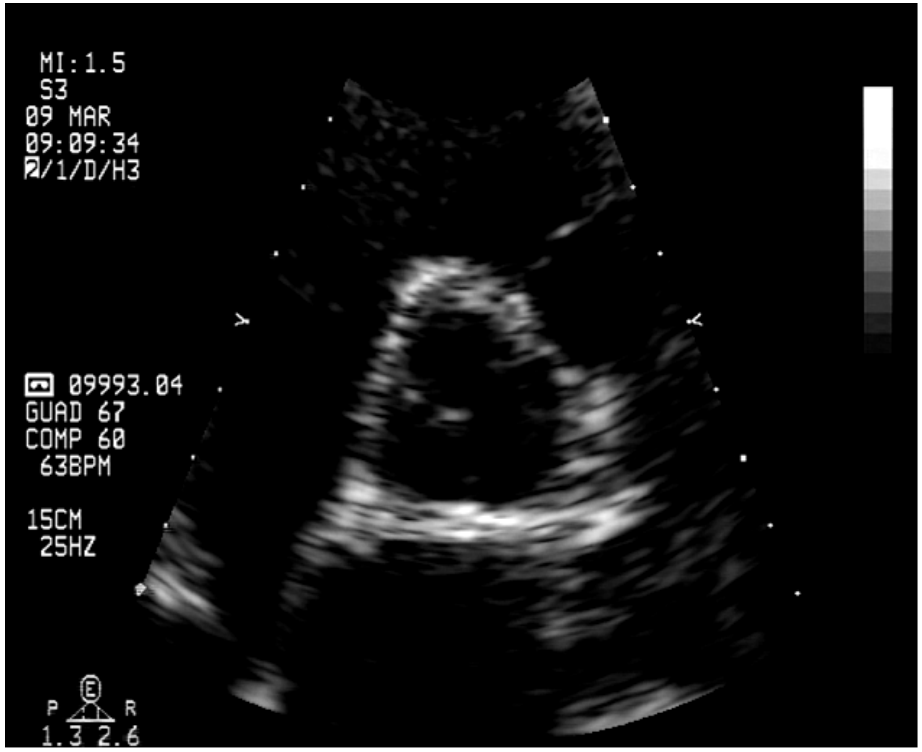
Coronary Artery Calcium Score

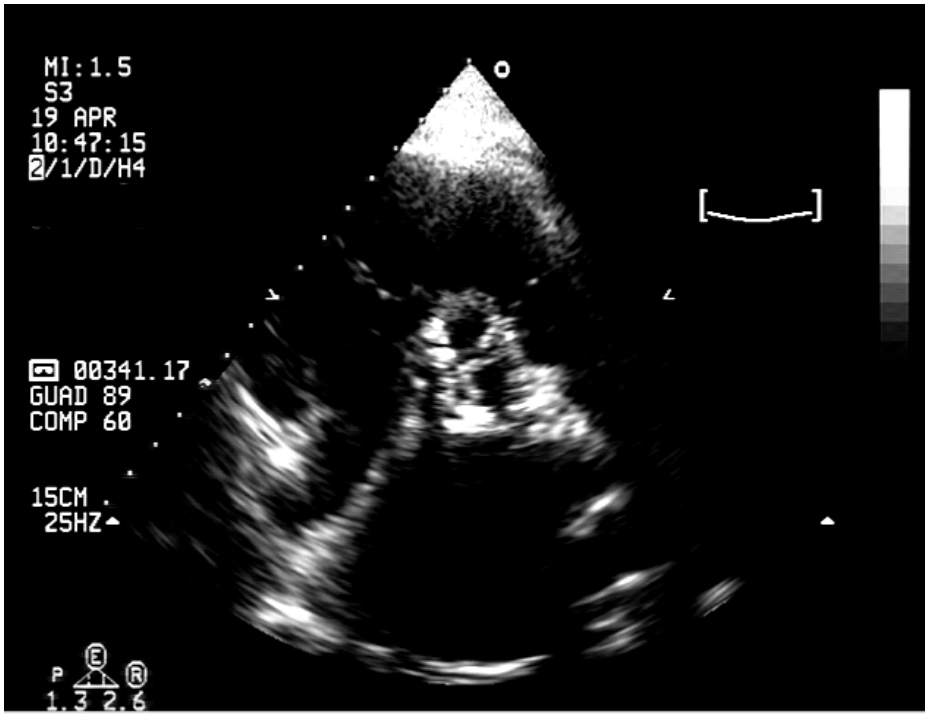




Sopravvivenza complessiva in 4474 uomini e 3219 donne con >1 fattore di rischio stratificati per Coronary Calcium Score

J Am Coll Cardiol. 2003 Jun 4;41(11):1886-98


MI:1.5
S3
09 MAR
09:09:34
2/1/D/H3
09993.04
GUAD 67
COMP 60
63BPM
15CM
25HZ
P
R
1.3 2.6


MI:1.5
S3
19 APR
10:47:15
2/1/D/H4
00341.17
GUAD 89
COMP 60
15CM
25HZ
P
R
1.3 2.6

Calcificazioni cardiache

Le calcificazioni cardiache sono frequentemente riscontrati nell'esame ecocardiografico di routine, sono generalmente sono asintomatiche e la loro prevalenza varia a seconda del sito valutato, dell'età, dei fattori di rischio CV(insufficienza renale, diabete…), terapie farmacologiche.

Il sito intracardiaco più frequentemente colpito con calcificazione sono la **valvola aortica** (prevalenza circa il 23%) e **l'anulus mitralico** (prevalenza 8-15%)

ASSOCIATION OF AORTIC-VALVE SCLEROSIS WITH CARDIOVASCULAR MORTALITY AND MORBIDITY IN THE ELDERLY

CATHERINE M. OTTO, M.D., BONNIE K. LIND, M.S., DALANE W. KITZMAN, M.D., BERNARD J. GERSH, M.B., CH.B., D.PHIL., AND DAVID S. SISCOVICK, M.D., M.P.H., FOR THE CARDIOVASCULAR HEALTH STUDY

TABLE 2. EVENT RATES IN THE THREE GROUPS.

EVENT	NORMAL AORTIC VALVES (N=3919)	AORTIC SCLEROSIS (N=1610)	AORTIC STENOSIS (N=92)	P VALUE FOR TREND
	number (percent)			
Death from any cause	583 (14.9)	353 (21.9)*	38 (41.3)*	<0.001
Death from cardiovascular causes	238 (6.1)	162 (10.1)*	18 (19.6)*	<0.001
Myocardial infarction†	217 (6.0)	123 (8.6)‡	9 (11.3)‡	<0.001
Angina†	358 (11.0)	160 (13.0)	17 (24.3)*	0.001
Congestive heart failure†	337 (8.9)	192 (12.6)*	21 (24.7)*	<0.001
Stroke†	238 (6.3)	122 (8.0)§	10 (11.6)§	0.003

Impact of aortic or mitral valve sclerosis and calcification on cardiovascular events and mortality: A meta-analysis ☆

Danitz
Nicola

Cardiovascular morbidity and mortality in patients with aortic valve sclerosis: A systematic review and meta-analysis

Check for updates

Matteo Nicola Dario , Mauro Pepi [c],
Elena Tremoli [c], Paol

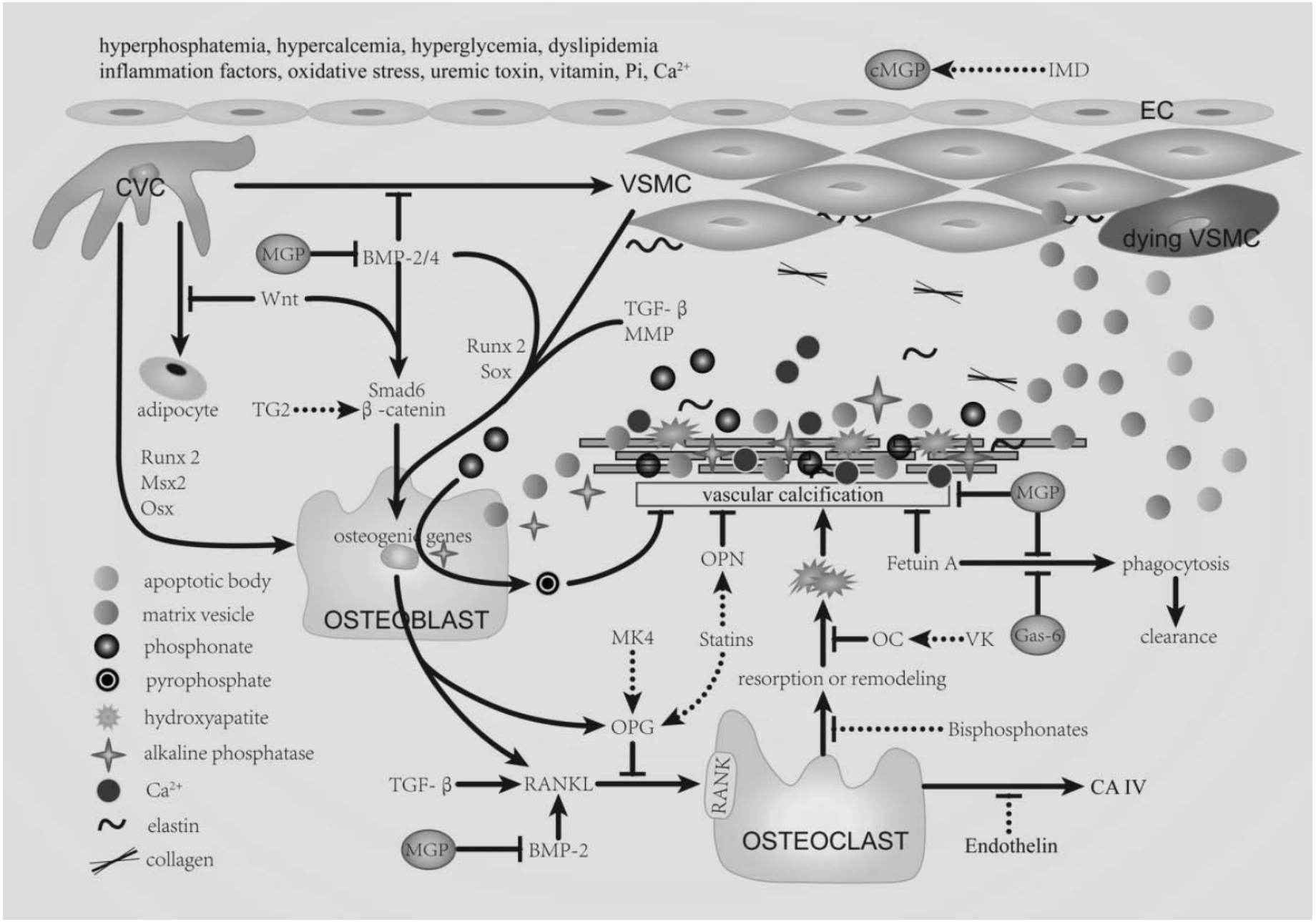
The Prevalence, Incidence, Progression, and Risks of Aortic Valve Sclerosis

A Systematic Review and Meta-Analysis

Sean Coffey, MBBS,*† Brian Cox, PHD,‡ Michael J. A. Williams, MD†
Oxford, United Kingdom; and Dunedin, New Zealand

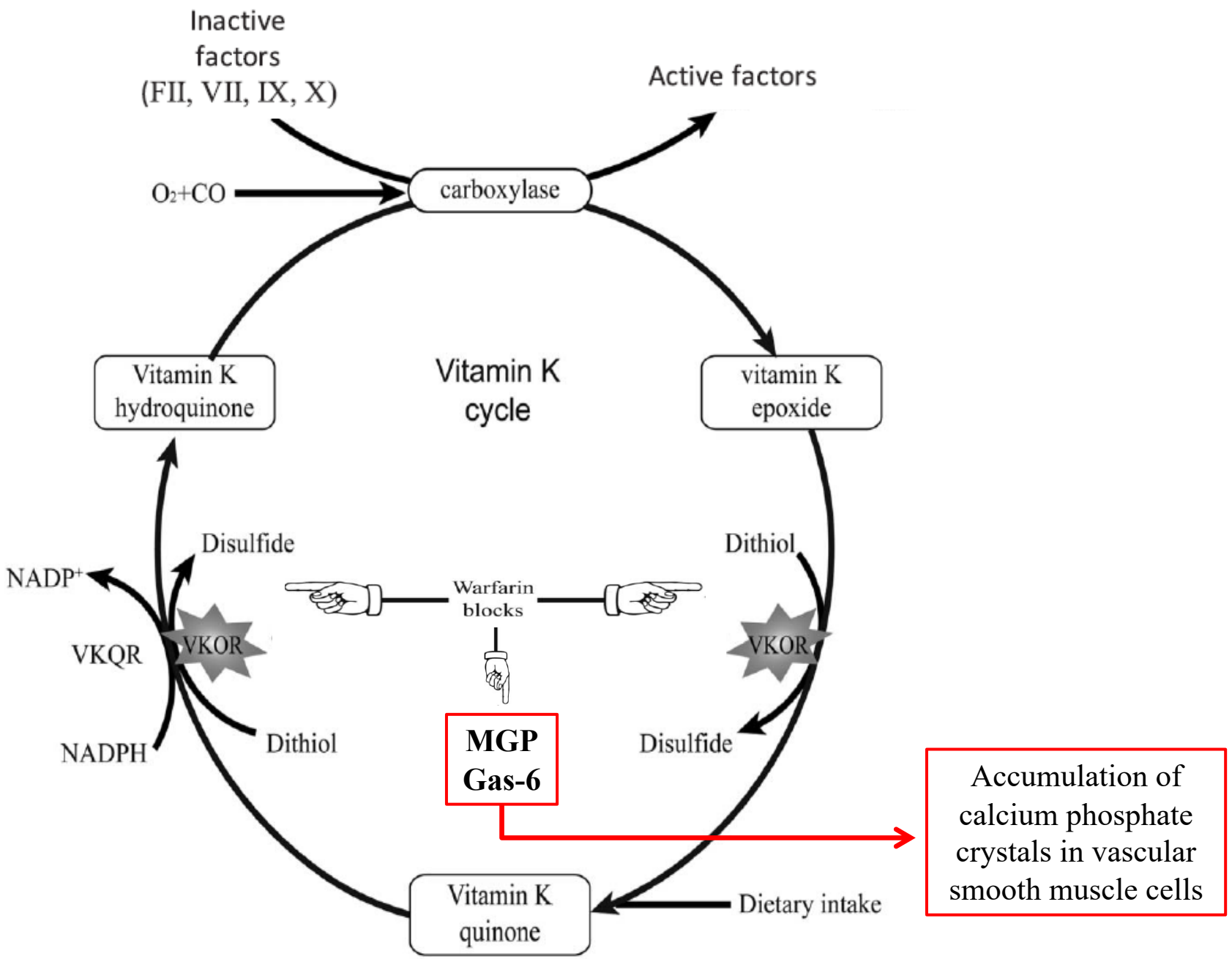
Risk Ratio [95% CI]

	Aortic valve lesion (AVC/AVS)			**Mitral valve lesions (MAC/MVC)**
	Pradelli et.Al	*Di Minno et.Al*	*Coffey et.Al*	*Pradelli et.Al*
All cause mortality	1.14 [1.01-1.30]	N/A	1,36 [1.17-1.59]	1.53 [1.24-1.89]
Cardiovascular mortality	1.53 [1.19-1.98]	1,41 [1.16-1.71]	1,69 [1.32-2.15]	1.65 [1.36-2.00]
Stroke	1.16 [0.91-1.48]	2,70 [1.45-5.01]	1,27 [1.01-1.60]	1.42 [1.15-1.75]
Myocardial infarction	1.24 [0.98-1.57]	N/A	N/A	1.40 [1.14-1.72]


hyperphosphatemia, hypercalcemia, hyperglycemia, dyslipidemia
inflammation factors, oxidative stress, uremic toxin, vitamin, Pi, Ca2+
cMGP
IMD
EC
CVC
VSMC
dying VSMC
MGP
BMP-2/4
Wnt
TGF- β
MMP
Runx 2
Sox
adipocyte
TG2
Smad6
β -catenin
Runx 2
Msx2
Osx
vascular calcification
MGP
osteogenic genes
OPN
Fetuin A
phagocytosis
apoptotic body
matrix vesicle
phosphonate
pyrophosphate
hydroxyapatite
alkaline phosphatase
Ca2+
elastin
collagen
OSTEOBLAST
MK4
Statins
OC
VK
Gas-6
clearance
resorption or remodeling
OPG
Bisphosphonates
TGF- β
RANKL
RANK
CA IV
MGP
BMP-2
OSTEOCLAST
Endothelin

Identificazione precoce di calcificazione cardiaca: biomarkers

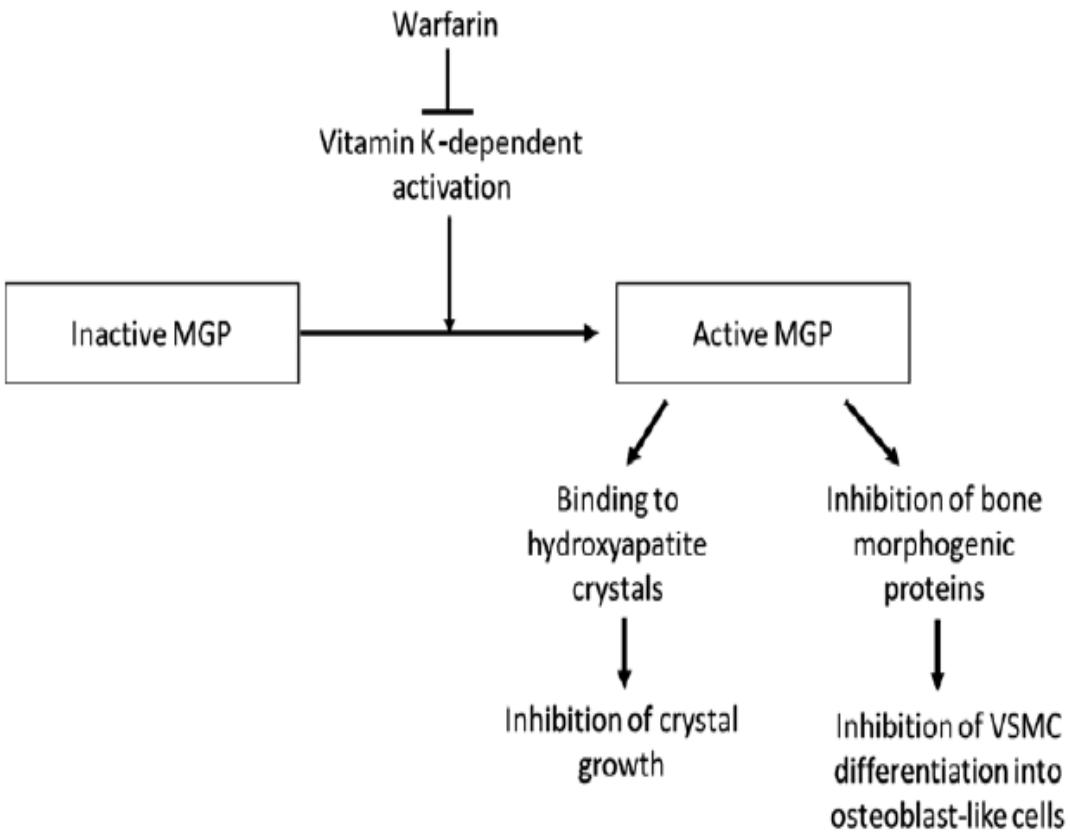
Fetuin-A (a2-Heremans-Schmid glycoprotein)	proteina multifunzionale sierica di sintesi epatica, ha un'alta affinità per il minerale osseo e previene la precipitazione di fosfati di calcio inibendo quindi la calcificazione dei tessuti.
Matrix Gla protein (MGP)	proteina a basso peso molecolare **vitamina K-dipendente** diffusamente espressa; svolge un ruolo importante nella prevenzione della calcificazione dei tessuti molli legando la proteina morfogenica dell'osso-2 (BMP2).
Growth arrest-specific protein 6 (Gas-6)	Proteina **vitamina K-dipendente** espressa nellle cellule muscolari liscie in grado di inibirne l'apoptosi.
Osteoprotegerin (OPG)	è una citochina della superfamiglia dei recettori del TNF, diffusamente espressa che regola osteoclastogenesi agendo come recettore di decoy per il recettore RANK
Klotho	proteina multifunzione coinvolta nella regolazione del metabolismo del fosfato di calcio



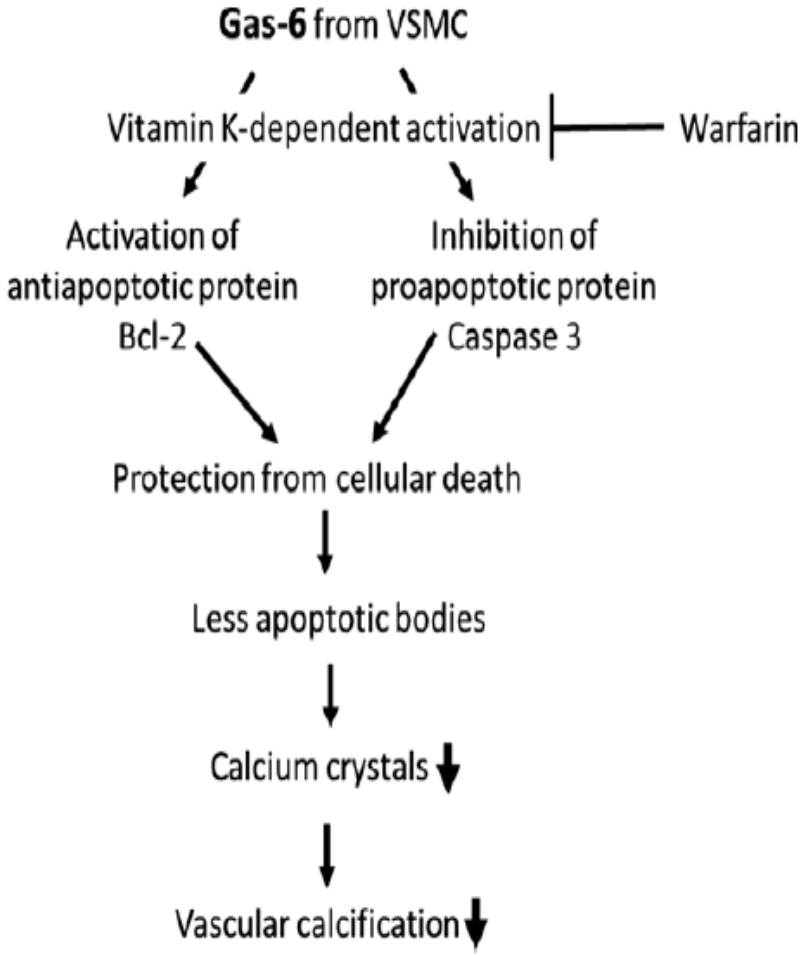
Accumulation of calcium phosphate crystals in vascular smooth muscle cells

Modificato da : J Cardiovasc Pharmacol 2014;63:76–82

Matrix Gla protein (MGP)



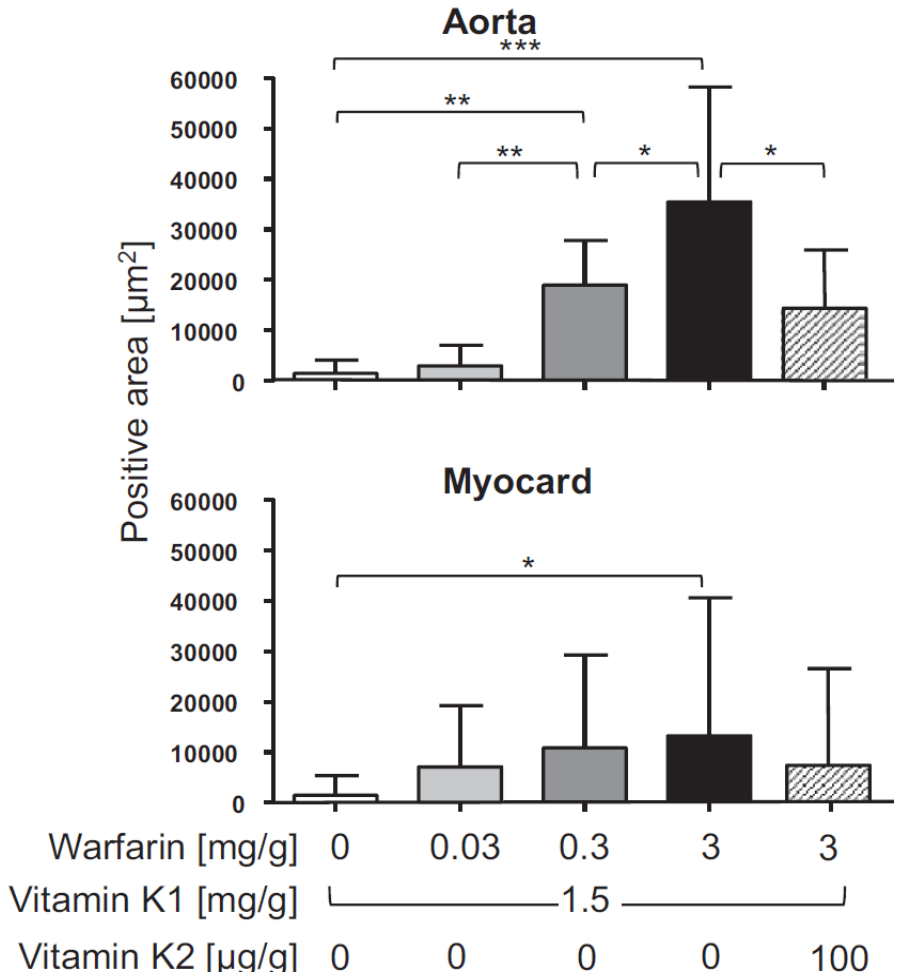
Growth arrest-specific protein 6 (Gas-6)



Basic & Clinical Pharmacology & Toxicology, 2018, 122, 19–24

Warfarin Induces Cardiovascular Damage in Mice

Thilo Krüger,* Stephan Oelenberg,* Nadine Kaesler, Leon J. Schurgers, Annette M. van de Sandt, Peter Boor, Georg Schlieper, Vincent M. Brandenburg, Bertalan C. Fekete, Verena Veulemans, Markus Ketteler, Cees Vermeer, Willi Jahnen-Dechent, Jürgen Floege, Ralf Westenfeld



Arterioscler Thromb Vasc Biol. 2013;33:2618-2624

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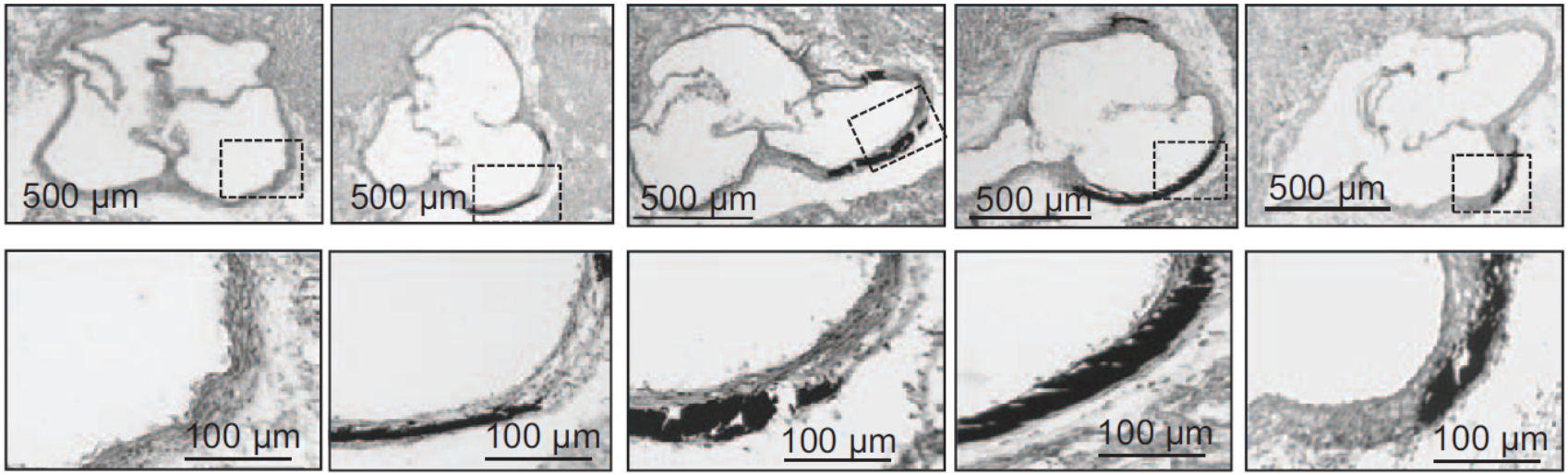


Warfarin [mg/g]	0	0.03	0.3	3	3
Vitamin K1 [mg/g]			1.5		
Vitamin K2 [µg/g]	0	0	0	0	100

Arterioscler Thromb Vasc Biol. 2013;33:2618-2624

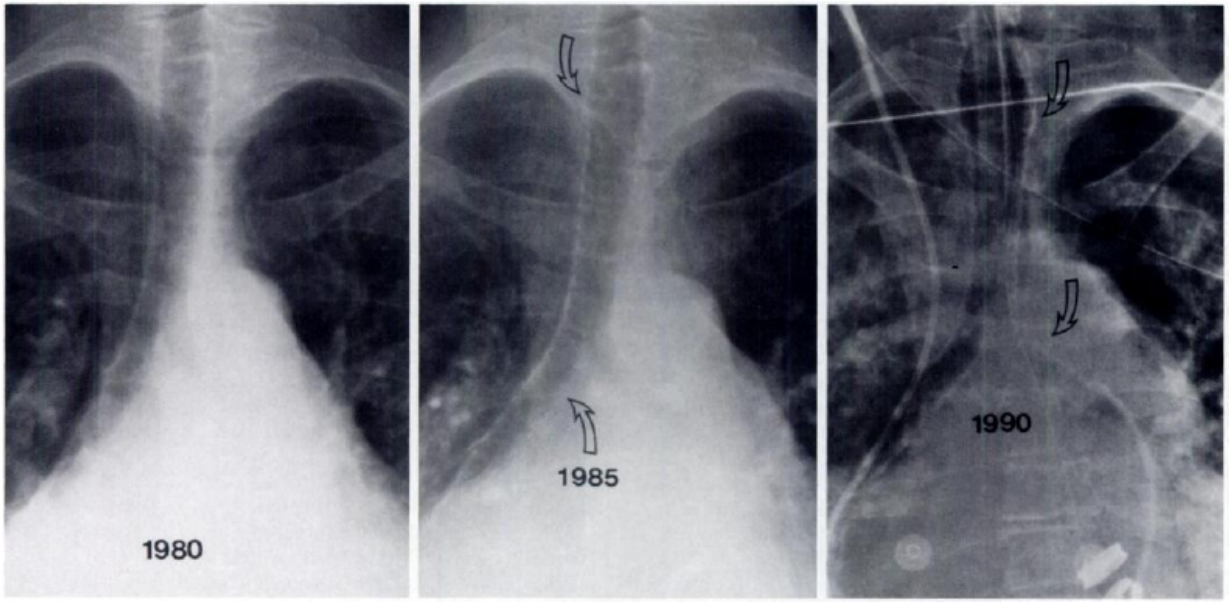
Tracheal and Bronchial Cartilaginous Rings: Warfarin Sodium—induced Calcification[1]

Rogelio M. Moncada, MD • Luz A. Venta, MD • Enrique R. Venta, PhD • Jawed Fareed, PhD
Jeanine M. Walenga, PhD • Harry L. Messmore, MD

Sono state analizzate radiografie del torace di 92 pazienti in terapia con warfarin e 105 pazienti come gruppo di controllo. La calcificazione degli anelli cartilaginei (CCR) è stata classificata come non presente (punteggio 0), sottile (punteggio 1) e ampia (punteggio 2).

	Warfarin *n* = 92 pz (%)	Controllo *n* = 105 pz (%)	p
CCR = 1 e 2	43 (47%)	20 (19%)	< 0,001
CCR = 2	23 (25%)	3 (3%)	< 0,001

Una correlazione positiva significativa (p<0,001) era presente anche tra la durata della terapia con warfarin e l'aumento dei livelli di CCR.



Radiology 1992;184:437-439

Warfarin use and the risk of valvular calcification

R. G. LERNER,* W. S. ARONOW,* A. SEKHRI,* C. PALANISWAMY,* C. AHN,† T. SINGH,* R. SANDHU* and J. A. MCCLUNG*

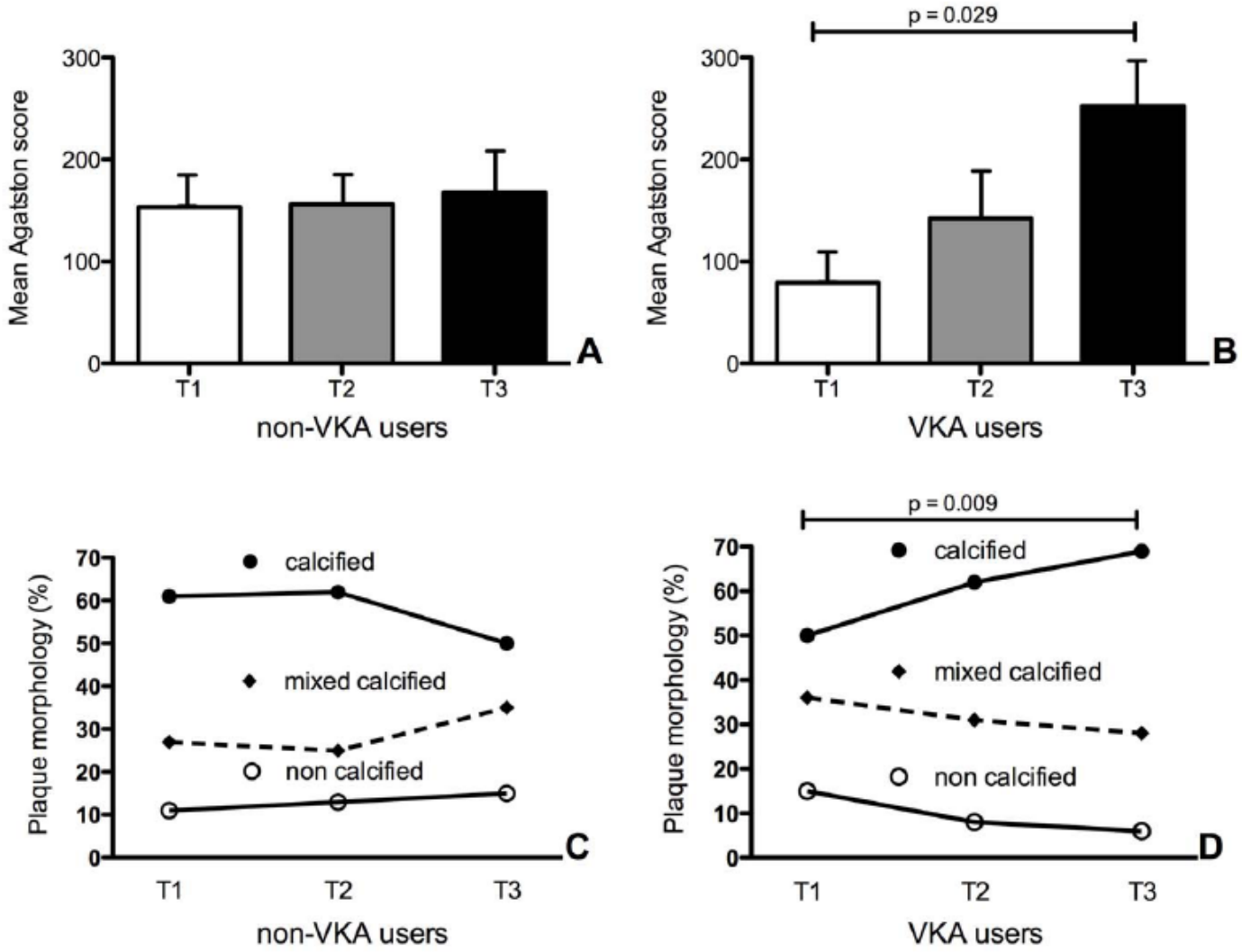
Objectives: To investigate the incidence of mitral valve calcium (MVC), mitral annular calcium (MAC) and aortic valve calcium (AVC) in patients with non-valvular atrial fibrillation (AF) treated with warfarin vs. no warfarin. *Patients and methods:* Of 1155 patients, mean age 74 years, with AF, 725 (63%) were treated with warfarin and 430 (37%) without warfarin. The incidence of MVC, MAC and AVC was investigated in these 1155 patients with two-dimensional echocardiograms. Unadjusted logistic regression analysis was

Variables	No warfarin (n = 430), %	Warfarin (n = 725), %	P-value	Odds ratio	95% CI
MVC	36 (8)	89 (12)	0.039	1.53	1.02–2.30
MAC	140 (33)	275 (38)	0.066	1.27	0.99–1.63
AVC	166 (39)	351 (48)	0.001	1.49	1.17–1.90
MVC or MAC or AVC	225 (52)	473 (65)	< 0.0001	1.71	1.34–2.18

Conclusions: Use of warfarin in patients with AF is associated with an increased prevalence of MVC, MAC or AVC.

J Thromb Haemost 2009; 7: 2023–7.

Vitamin K-Antagonists Accelerate Atherosclerotic Calcification and Induce a Vulnerable Plaque Phenotype



Schurgers LJ et al. PLoS One. 2012;7(8):e43229

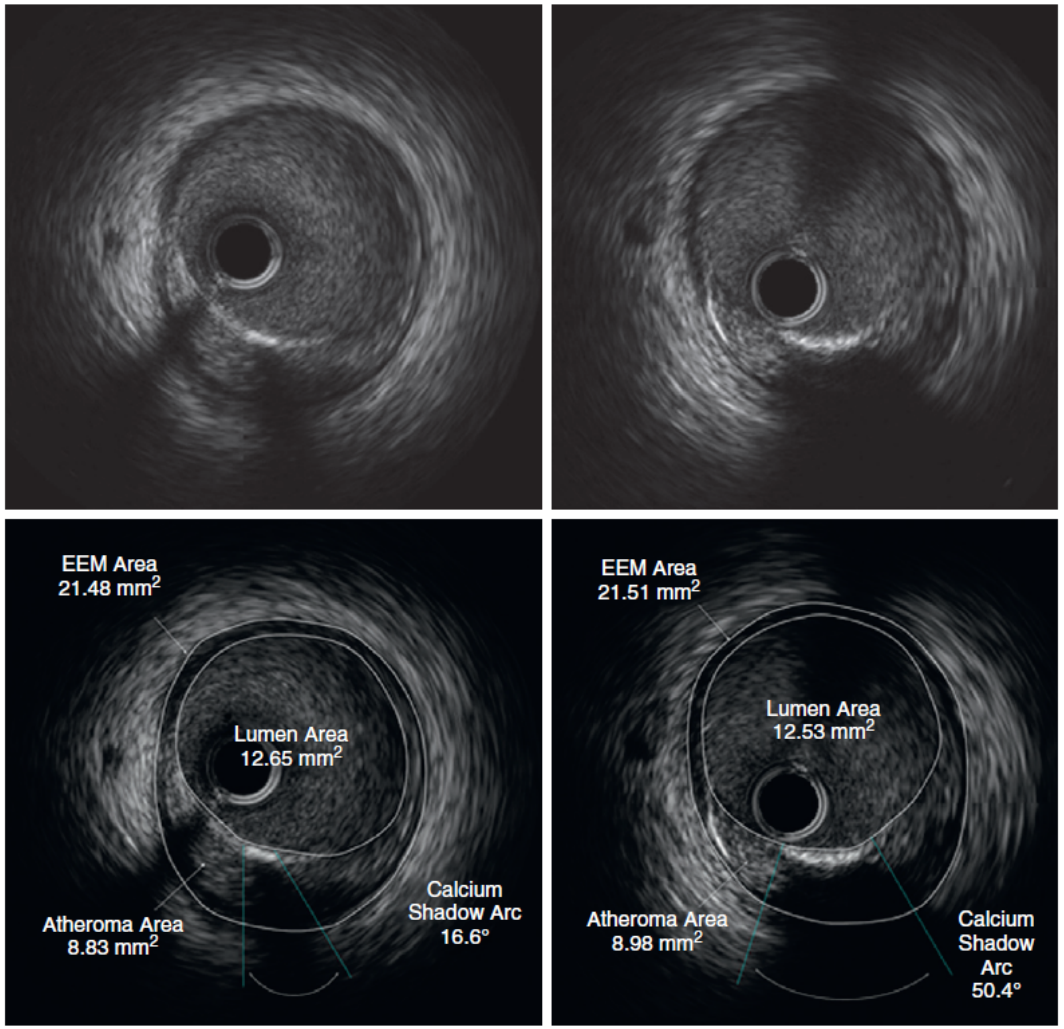
Warfarin Use Is Associated With Progressive Coronary Arterial Calcification

Insights From Serial Intravascular Ultrasound

Analisi post-hoc: 8 studi randomizzati prospettici che utilizzano la tecnica IVUS.

Sono state valutate: Percent Atheroma Volume (PAV) e Calcium Index (CaI) in segmenti coronarici corrispondenti in pazienti con malattia coronarica trattati con Warfarin (n = 171) vs gruppo di controllo (n = 4.129)

Follow-up: 18 - 24 mesi.



JACC Cardiovasc Imaging. 2018 Sep;11(9):1315-1323

Warfarin Use Is Associated With Progressive Coronary Arterial Calcification

Insights From Serial Intravascular Ultrasound

Calcium Index	Overall (n = 4,300)	Warfarin (n = 171)	No Warfarin (n = 4,129)	Difference *t* Statistic	p Value for Difference
Baseline	0.28 (0.09, 0.54)	0.30 (0.14, 0.59)	0.28 (0.09, 0.54)	2.3	p = 0.024*
Change from baseline	0.04 (0.00, 0.11)	0.05 (0.00, 0.15)	0.04 (0.00, 0.11)	3.9	p < 0.001†
p value for test of change = 0‡	<0.001	<0.001	<0.001		
Annualized changes	0.02 (0.00, 0.06)	0.03 (0.00, 0.08)	0.02 (0.00, 0.06)	4.2	p < 0.001§

CONCLUSIONS

In conclusion, warfarin use is independently associated with serial procalcific effects within the human coronary vasculature in vivo, irrespective of concomitant changes in atheroma volume, concomitant statin therapy, and renal function. These findings are consistent with earlier preclinical and cross-sectional human vascular imaging data. The longer-term clinical implications of these data and their extrapolation to newer oral anticoagulant agents remain unknown, however, thus warranting further investigation.

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with angiographically apparent coronary artery disease, warfarin use is associated with progressive coronary artery calcification in vivo, independent of its baseline extent, the degree of baseline plaque burden, baseline or concomitant statin use, or renal function.

JACC Cardiovasc Imaging. 2018 Sep;11(9):1315-1323

Valutazione della calcifilassi coronarica **I**n pazienti a medio-elevato rischio cardiovascolare sottoposti a TC coro**N**arica in terapia anticoagulante orale per fibrillazione atriale non valvolare: V**K**A vs DO**A**Cs

Scopo dello studio

Lo scopo dello studio è valutare, mediante TC coronarica, la presenza di calcio coronarico in una **popolazione a medio-elevato rischio cardiovascolare** con fibrillazione atriale non valvolare (FANV) in terapia con anticoagulanti diretti (DOACs) *vs* farmaci anticoagulanti VKA.

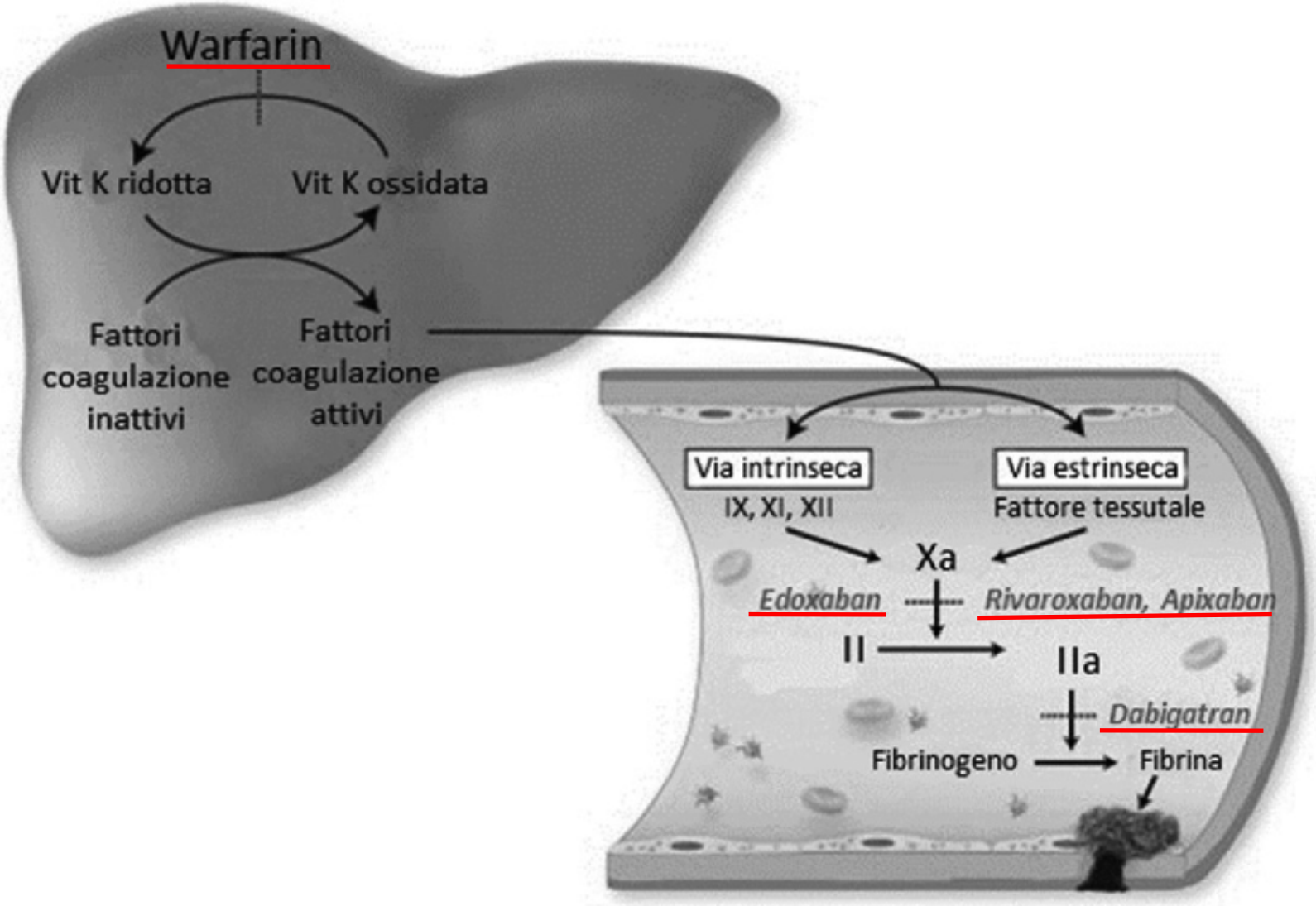
VINKA TRIAL

Razionale dello studio

Il razionale dello studio si fonda sulla concreta possibilità di **limitare**, nei pazienti affetti da FANV (ed eventualmente in terapia per tromboembolismo venoso), **il fenomeno della calcifilassi indotto dai farmaci anticoagulanti VKA** alla luce del meccanismo d'azione totalmente diverso rispettivamente di dabigatran (inibitore diretto della trombina), apixaban, rivaroxaban ed edoxaban (inibitori diretti del fattore Xa).

VINKA TRIAL

Differenti meccanismi d'azione

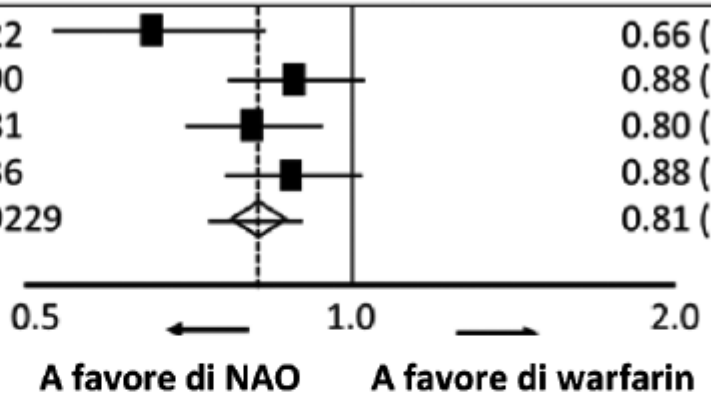


G Ital Cardiol 2015;16(11 Suppl 1):3S-16S

Efficacia e sicurezza dei DOACs

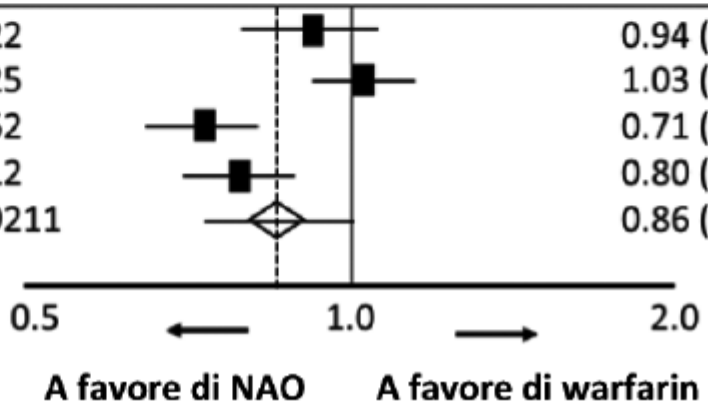
Ictus o eventi embolici

	NAO (eventi)	Warfarin (eventi)	RR (95% IC)	P
RE-LY	134/6076	199/6022	0.66 (0.53-0.82)	0.0001
ROCKET AF	269/7081	306/7090	0.88 (0.75-1.03)	0.12
ARISTOTLE	212/9120	265/9081	0.80 (0.67-0.95)	0.012
ENGAGE AF-TIMI 48	296/7035	337/7036	0.88 (0.75-1.02)	0.10
Combinati	911/29312	1107/29229	0.81 (0.73-0.91)	<0.0001



Sanguinamenti maggiori

	NAO (eventi)	Warfarin (eventi)	RR (95% IC)	P
RE-LY	375/6076	397/6022	0.94 (0.82-1.07)	0.34
ROCKET AF	395/7111	386/7125	1.03 (0.90-1.18)	0.72
ARISTOTLE	327/9088	462/9052	0.71 (0.61-0.81)	<0.0001
ENGAGE AF-TIMI 48	444/7012	557/7012	0.80 (0.71-0.90)	0.0002
Combinati	1541/29287	1802/29211	0.86 (0.73-1.00)	0.06



Modificata da Ruff et al. G Ital Cardiol 2015;16(11 Suppl 1):3S-16S

Materiali e Metodi

Dimensione del campione:
L'obiettivo è di ottenere un campione complessivo minimo di 100 pazienti (50 pazienti in terapia con VKA e 50 pazienti in terapia con DOACs)

Criteri di inclusione:
- Età: ≥ 18 anni e ≤ 100 anni.
- Firma del consenso informato
- Assunzione di terapia con VKA o DOACs per FANV da almeno 2 anni al momento dell'esecuzione della TC delle coronarie.
- Presenza di almeno 2 fattori di rischio cardiovascolari quali: familiarità per CAD precoce, tabagismo, ipertensione arteriosa, dislipidemia, diabete mellito, IRC (GFR<60 ml/min).
- Eseguita TC coronarica per ragioni cliniche con valutazione del Calcium score

Criteri di Esclusione:
- Assunzione di terapia con VKA o DOACs per tromboembolismo venoso.
- Assunzione di terapia anticoagulante con VKA e/o DOASc < di 2 anni dal momento dell'esecuzione della TC delle coronarie.
- Non allergie al mezzo di contrasto.
- Pregresso evento coronarico (NSTEMI-STEMI).
- Pregressa rivascolarizzazione coronarica sia essa chirurgica che percutanea.
- Stato di gravidanza.

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Scheda raccolta dati

TC coronarica eseguita in data _ _ /_ _ _/_ _ _ _

Motivo: □ controllo in asintomatico
□ controllo in sintomatico
□ pregresso esame dubbio

Eseguito m.d.c. □ si → Agatston score _____
□ no

DATI PAZIENTE:

Peso: _____Kg BMI: _____Kg/mq

Altezza: _____cm

Creatinina: _____ mg/dL GFR: _____ml/min/1,73 mq

Diabete □ Si □ No

Ipercolesterolemia □ Si □ No

Ipertensione □ Si □ No

Tabagismo □ Si □ No □ Ex

CAD pregressa □ Si □ No

Familiarità per CAD □ Si □ No

Terapia anticoagulante in atto per:
□ FANV
□ Protesi meccanica
□ Embolia polmonare/TVP

Tipo di terapia anticoagulante orale in atto

VKA	DOACs	
□ Warfarin	□ Dabigatran	□ 150 mg b.i.d □ 110 mg b.i.d.
□ Acenocumarolo	□ Rivaroxaban	□ 20 mg o.d. □ 15 mg o.d.
	□ Apixaban	□ 5 mg b.i.d □ 2.5 mg b.i.d.
	□ Edoxaban	□ 60 mg o.d □ 30 mg o.d.
↓	↓	↓
In terapia dal (mese/anno)	In terapia dal (mese/anno)	E' stato necessario **ridurre** dose
_ _ _/_ _ _ _	_ _ _/_ _ _ _	□ Si Quando?_ _/_ _ _/_ _ _ _ Perché?

Altre variazioni (Quando e perche):

_ _/_ _ _/_ _ _ _ _____

_ _/_ _ _/_ _ _ _ _____

_ _/_ _ _/_ _ _ _ _____

□ Variazione Cl Cr
□ Variazioni di peso
□ Eventi avversi _____
□ Altro _____

E' stato necessario **aumentare** dose

□ Si Quando?_ _/_ _ _/_ _ _ _ Perché?
□ Variazione Cl Cr
□ Variazioni di peso
□ Altro _____

N° Centro/N°Identificativo pz/ Iniziali pz	Sesso	Data di nascita	Data Valutazione
_ _ _/_ _ _ _/_ _	□ M □ F	_ _/_ _ _/_ _ _ _	_ _/_ _ _/_ _ _ _

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calfort


Pradaxa 110 mg
Pradaxa 150 mg
Xarelto 15 mg
Eliquis 5 mg
Daiichi-Sankyo
Lixiana 60 mg
Filmtabletten
edoxaban

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TRIAL

Sei interessato?
Contattami!

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Grazie!!!