



Conoscere e Curare il Cuore

2018

SABATO 17 MARZO

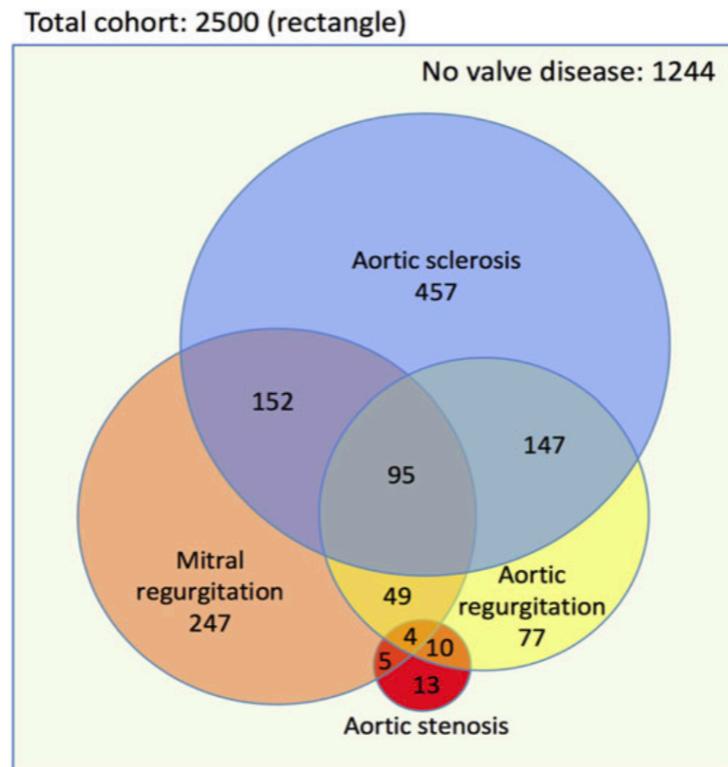
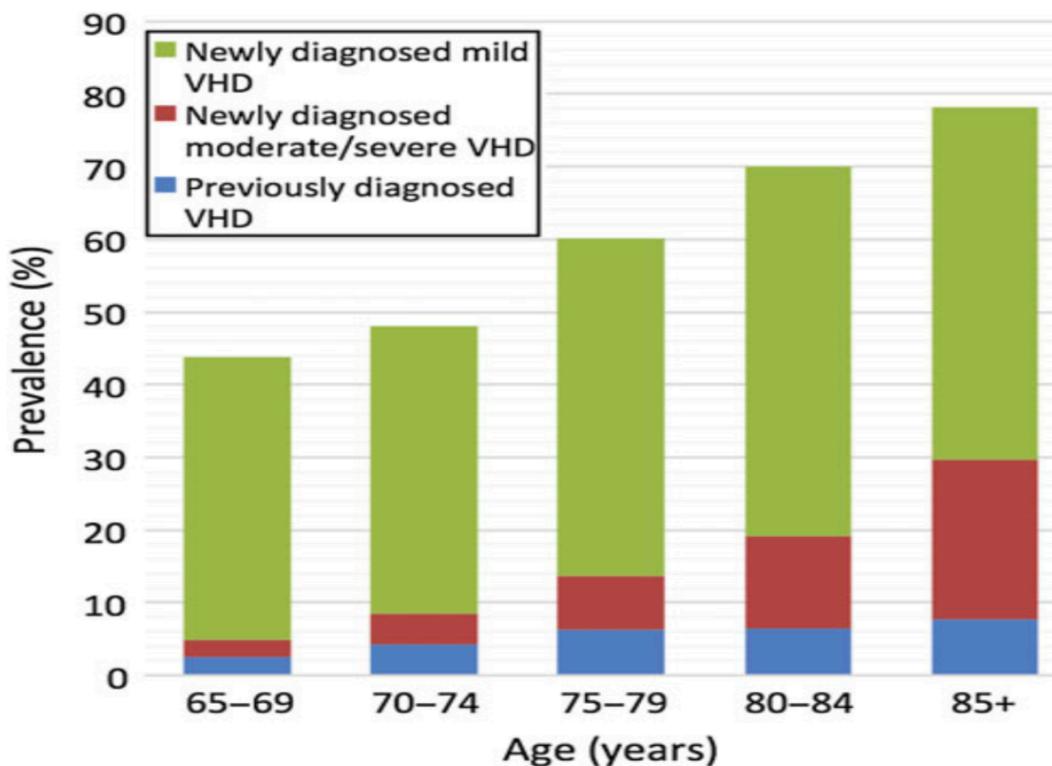
**LA STENOSI AORTICA DELL'ANZIANO SI PUO'
PREVENIRE. VECCHI FATTORI DI RISCHIO PER UNA
NUOVA PATOLOGIA**

Giuseppe Di Pasquale

*Unità Operativa di Cardiologia
Ospedale Maggiore, Bologna*



Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxVALVE Population Cohort Study[†]



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

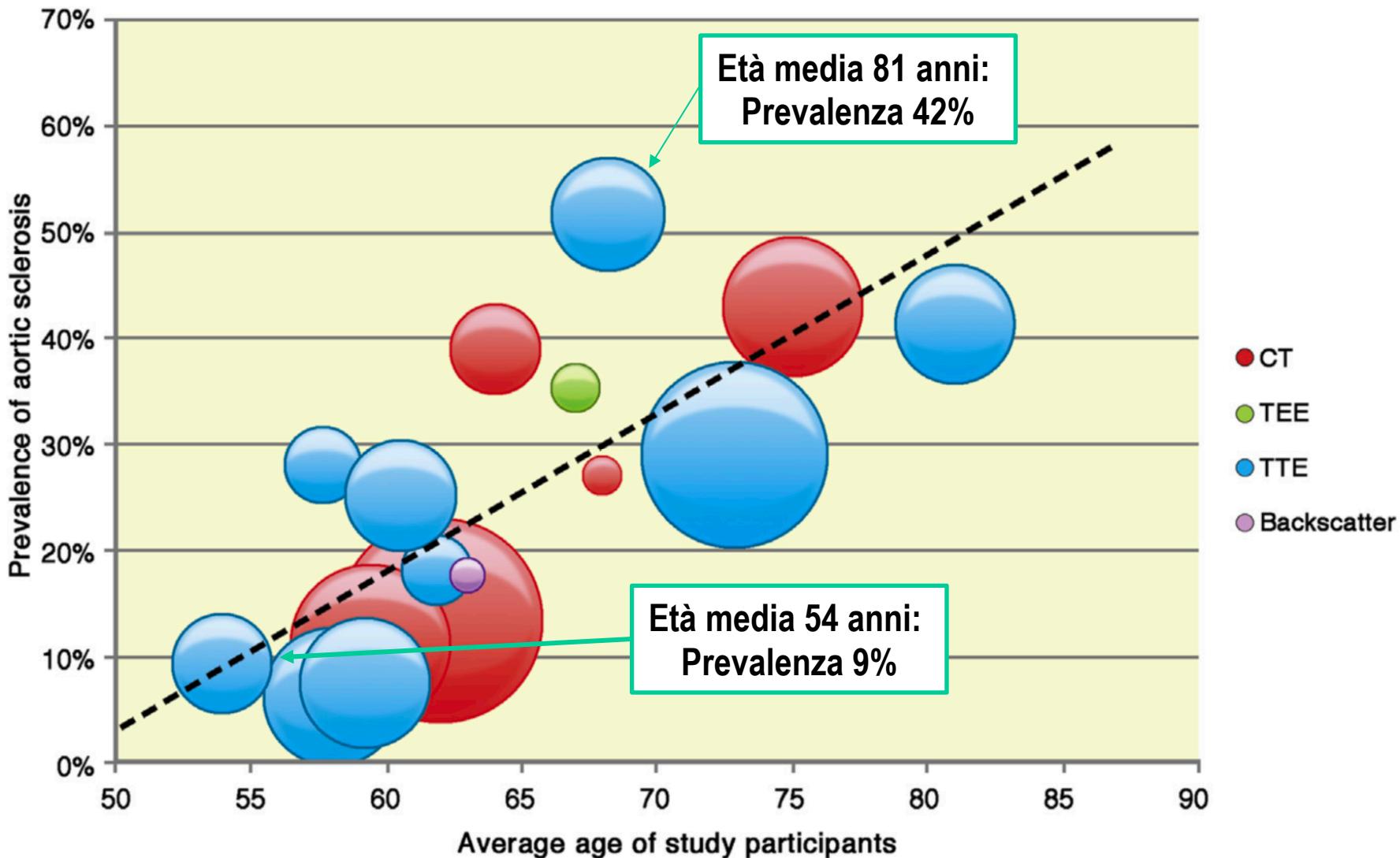
A Systematic Review and Meta-Analysis



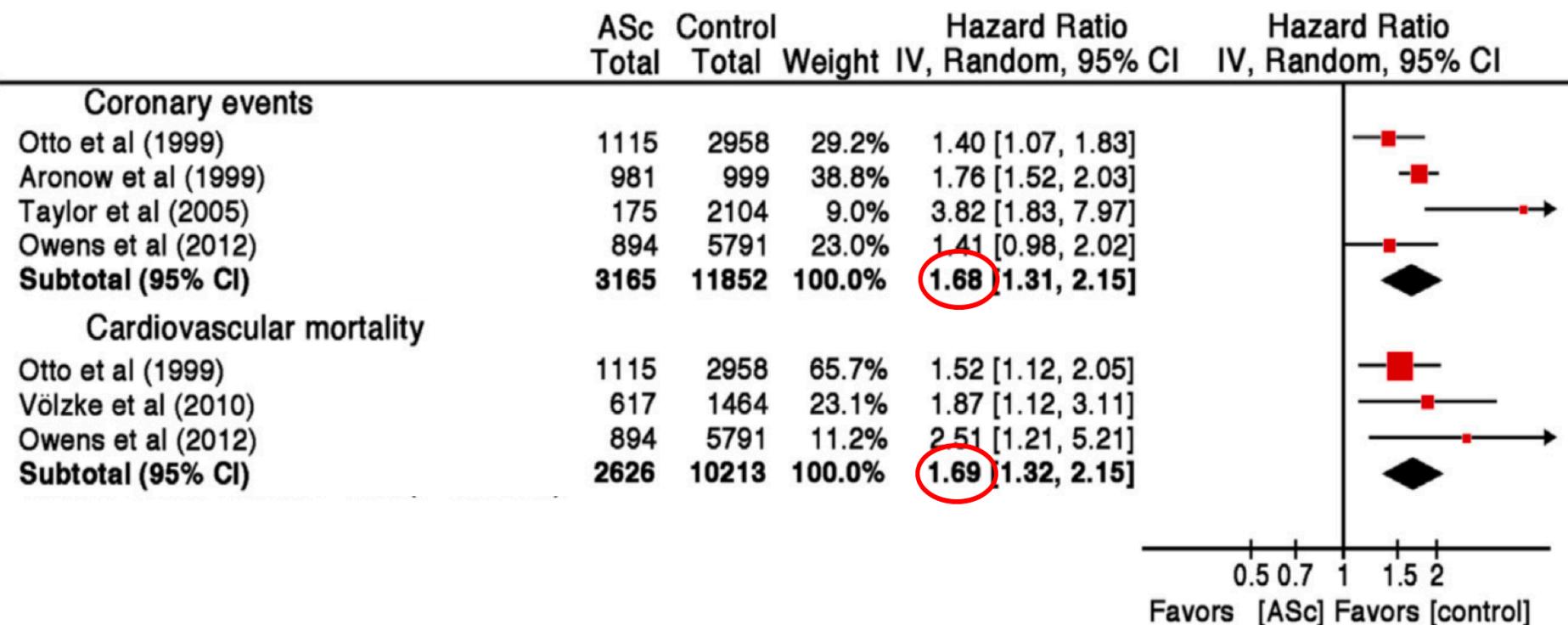
Sean Coffey, MBBS,*† Brian Cox, PhD,‡ Michael J. A. Williams, MD†

Oxford, United Kingdom; and Dunedin, New Zealand

Prevalence of Aortic Valve Sclerosis



Aortic Sclerosis and CV Events



Coffey et al, J Am Coll Cardiol 2014; 63:2852-61

Stenosi Aortica Degenerativa & Prevenzione

Agenda

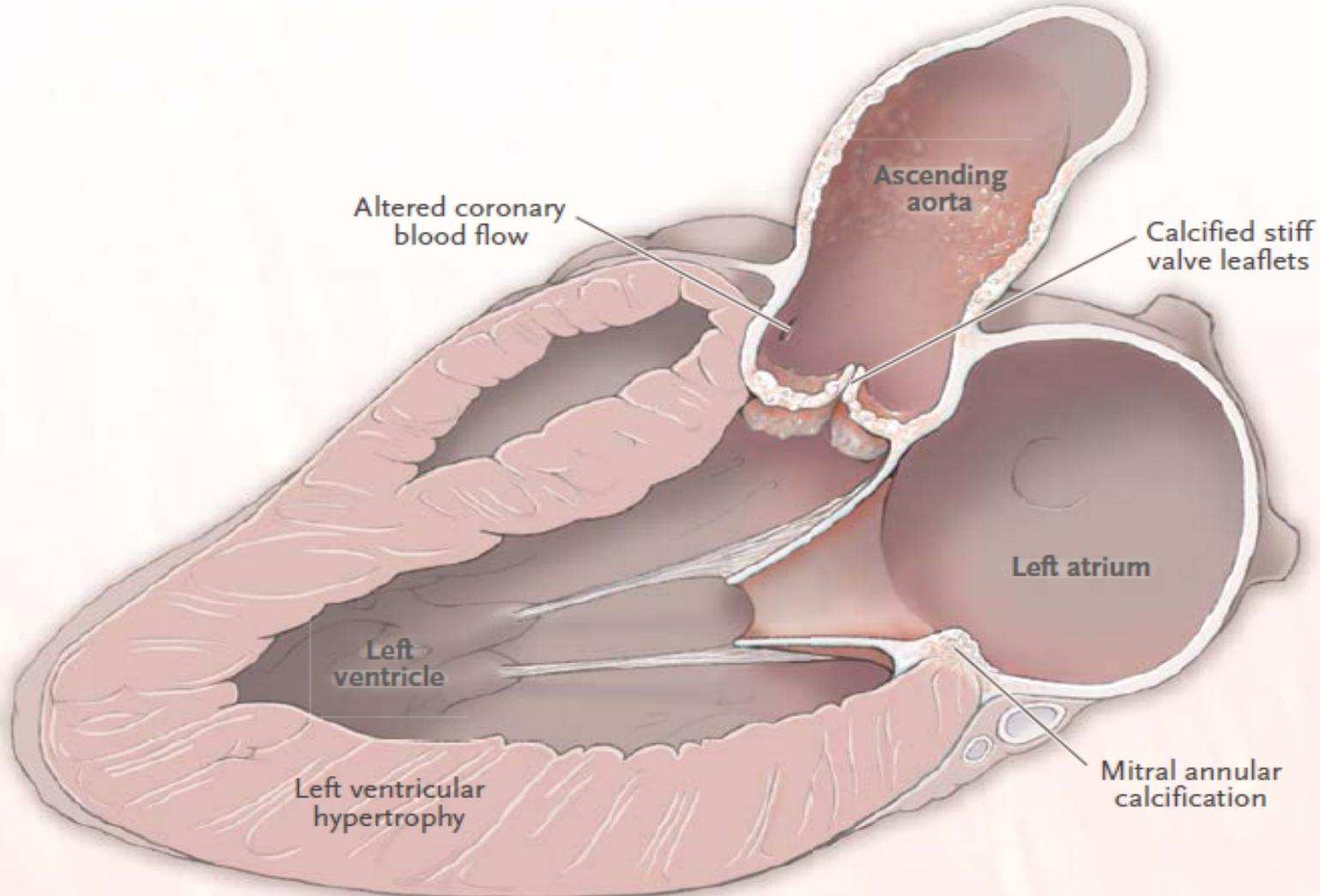
- **Meccanismi patogenetici**
- **Fattori di rischio predisponenti**
- **Interventi di prevenzione**

Stenosi Aortica Degenerativa & Prevenzione

Agenda

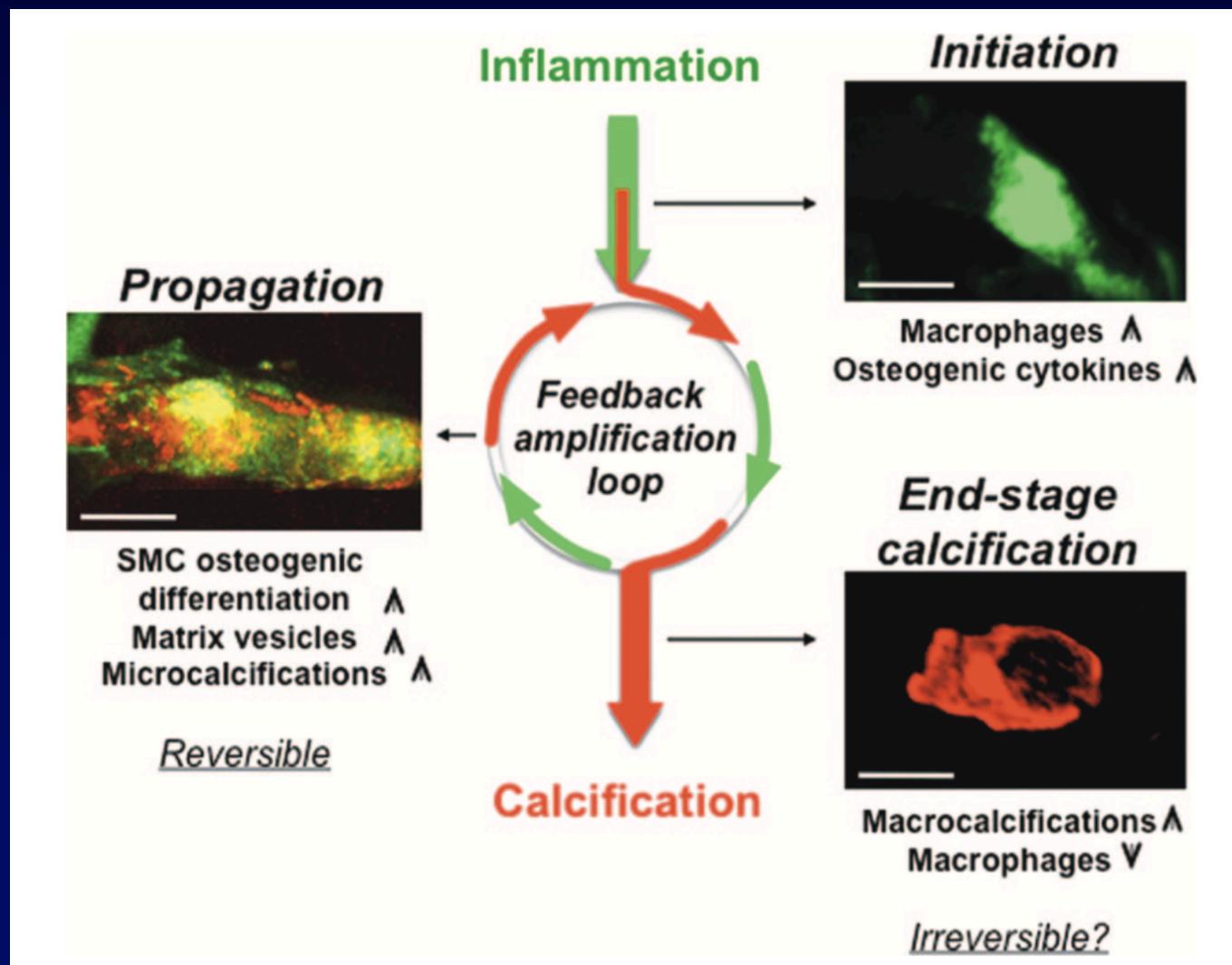
- Meccanismi patogenetici
- Fattori di rischio predisponenti
- Interventi di prevenzione

“Aortic Stenosis as a Systemic Disease”



Aortic Valve Stenosis From Patients at Risk to Severe Valve Obstruction
Otto CM et al. NEJM 2014; 371:744-56

Molecular Imaging of Cardiovascular Calcifications



Stenosi Aortica Degenerativa & Prevenzione

Agenda

- Meccanismi patogenetici
- Fattori di rischio predisponenti
- Interventi di prevenzione

Fattori di Rischio Clinici Associati a SAO

Età avanzata	Ipercolesterolemia familiare
Sesso maschile	Fosfati sierici elevati
Fumo di sigaretta	Calcio sierico elevato
Ipertensione	Insuficienza renale
Diabete mellito	Osteoporosi
Sindrome metabolica	Deficit di vitamina K
Obesità	Iperomocisteinemia
Adiposità addominale	PCR elevata
Elevati livelli LDL e lipoproteina (a)	Storia di irradiazione mediastinica
Ipertrigliceridemia	Componente genetica

Clinical Factors Associated With Calcific Aortic Valve Disease

B. FENDLEY STEWART, MD, FACC, DAVID SISCOVICK, MD, MPH, BONNIE K. LIND, MS,
JULIUS M. GARDIN, MD, FACC,* JOHN S. GOTTDIENER, MD, FACC,†
VIVIENNE E. SMITH, MD,‡ DALANE W. KITZMAN, MD, FACC,§
CATHERINE M. OTTO, MD, FACC, FOR THE CARDIOVASCULAR HEALTH STUDY||

Seattle, Washington; Orange, California; Washington, D.C.; Winston-Salem, North Carolina; and Albany, New York

J Am Coll Cardiol 1997; 29:630-634

Clinical Factors Associated With Aortic Stenosis

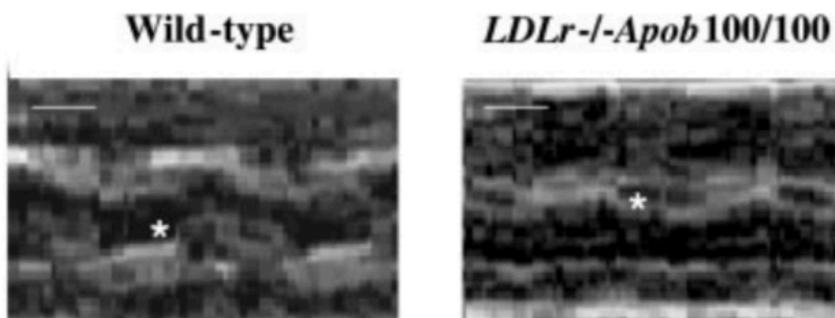
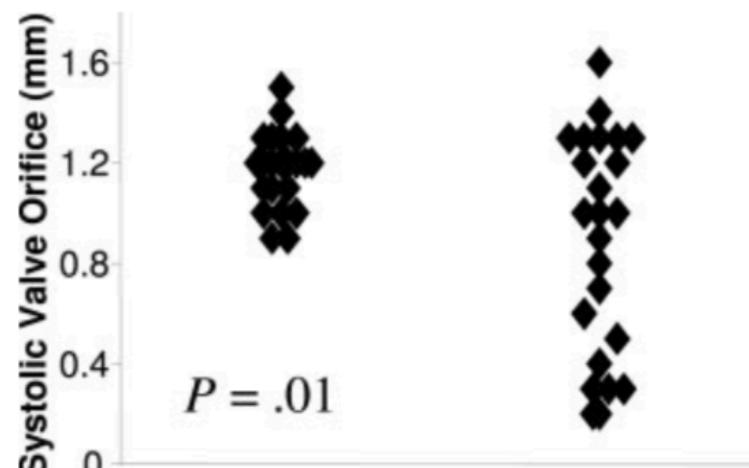
5201 pz \geq 65 anni arruolati nel Cardiovascular Health Study

Variable	p Value	Odds Ratio	95% Confidence Limits
Age	<0.001	2.18*	2.15, 2.20
Male gender	<0.001	2.03	1.7, 2.5
Lp(a)	<0.001	1.23†	1.14, 1.32
Height (cm)	0.001	0.84‡	0.75, 0.93
History of hypertension	0.002	1.23	1.1, 1.4
Present smoking	0.006	1.35	1.1, 1.7
LDLc (mg/dl)	0.008	1.12†	1.03, 1.23

Valvular Heart Disease

Calcific Aortic Valve Stenosis in Old Hypercholesterolemic Mice

Robert M. Weiss, MD*; Masuo Ohashi, MD*; Jordan D. Miller, PhD;
Stephen G. Young, MD; Donald D. Heistad, MD



The NEW ENGLAND JOURNAL *of* MEDICINE

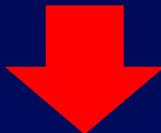
ESTABLISHED IN 1812

FEBRUARY 7, 2013

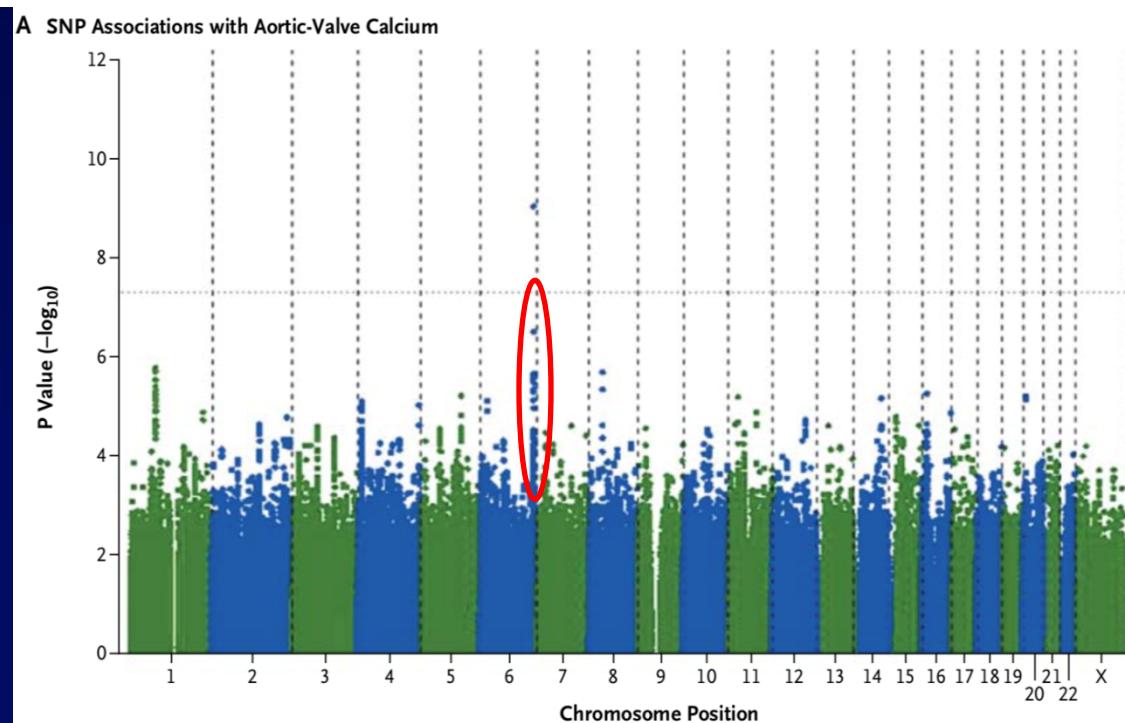
VOL. 368 NO. 6

Genetic Associations with Valvular Calcification and Aortic Stenosis

Analisi genoma in 6942 pax.
sottoposti a TC torace



correlazione tra variante
genica correlata ad aumento
Lipoproteina(a)
e calcificazione valvolare
aortica



Thanassoulis G et al NEJM 2013; 368:503-12

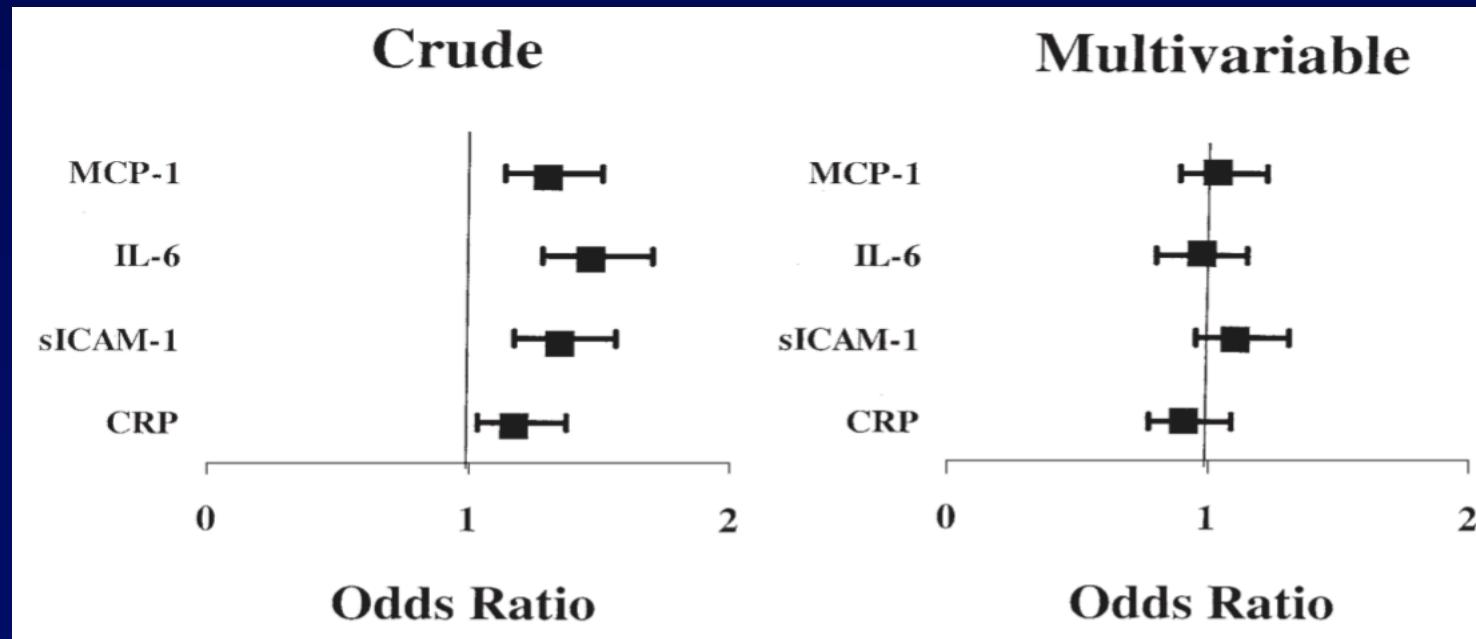
Relations of Inflammation and Novel Risk Factors to Valvular Calcification

Caroline S. Fox, MD, MPH^{a,f,g,*}, Chao-Yu Guo, PhD^a, Martin G. Larson, ScD^a,
Ramachandran S. Vasan, MD^{a,c,d}, Helen Parise, PhD^e,
Christopher J. O'Donnell, MD, MPH^{a,b,g}, Ralph B. D'Agostino, Sr., PhD^{a,e},
John F. Keaney, Jr., MD^c, and Emelia J. Benjamin, MD, ScM^{a,c,d}

2.683 soggetti studio Framingham (8,2% calcificazione anulus mitralico o aortico)

→ incremento significativo marker infiammatori nei pz con calcificazioni valvolari

→ perdita di significatività dopo aggiustamento per FR cardiovascolari



Features of the Metabolic Syndrome and Diabetes Mellitus as Predictors of Aortic Valve Calcification in the Multi-Ethnic Study of Atherosclerosis

Ronit Katz, PhD; Nathan D. Wong, PhD; Richard Kronmal, PhD; Junichiro Takasu, MD, PhD;
David M. Shavelle, MD; Jeffrey L. Probstfield, MD; Alain G. Bertoni, MD, MPH;
Matthew J. Budoff, MD; Kevin D. O'Brien, MD

6780 soggetti senza storia di CAD

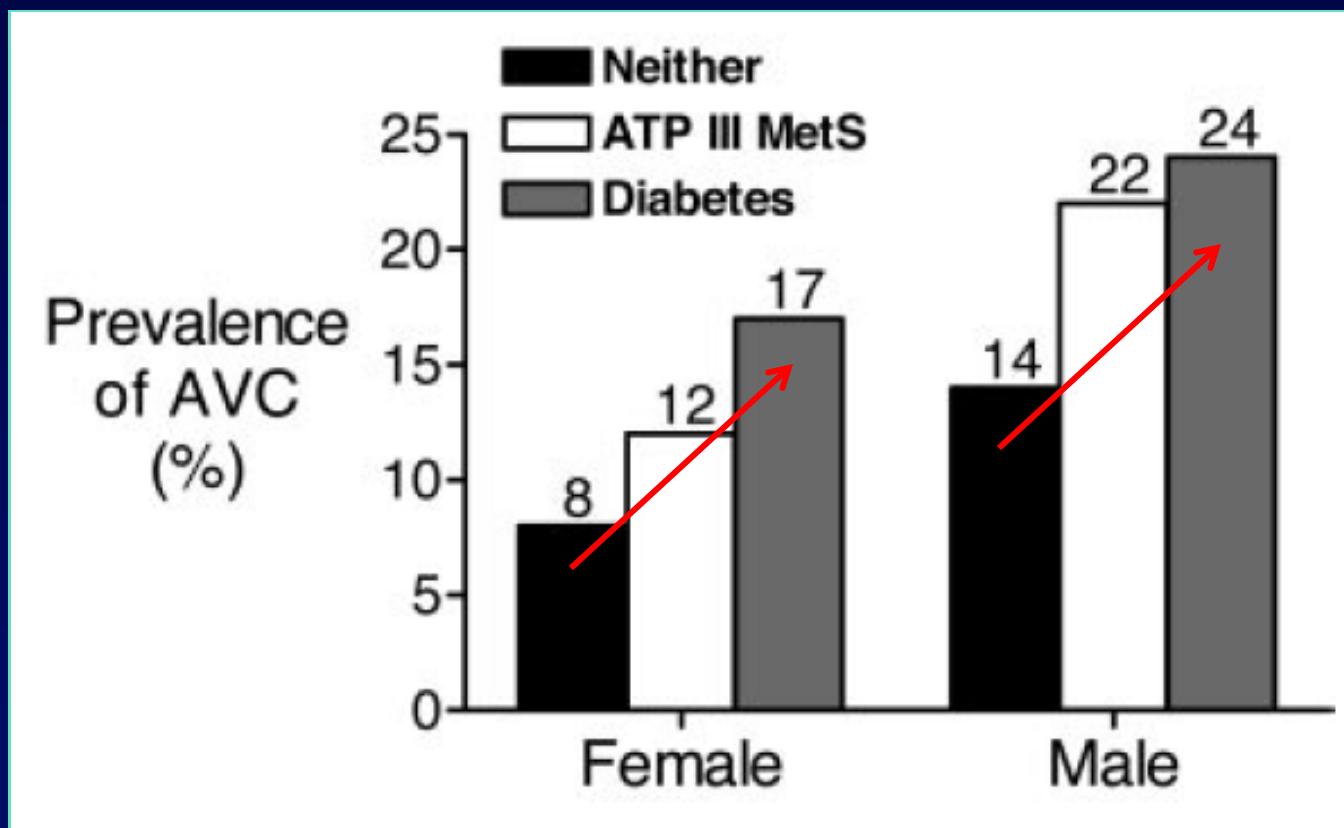
-1550 con sindrome metabolica

-1016 con diabete mellito

-4024 senza entrambi

sottoposti a determinazione TC del Calcium Score

Prevalence of AVC by Diabetes Mellitus or MetS





Association Between Cardiovascular Risk Factors and Aortic Stenosis

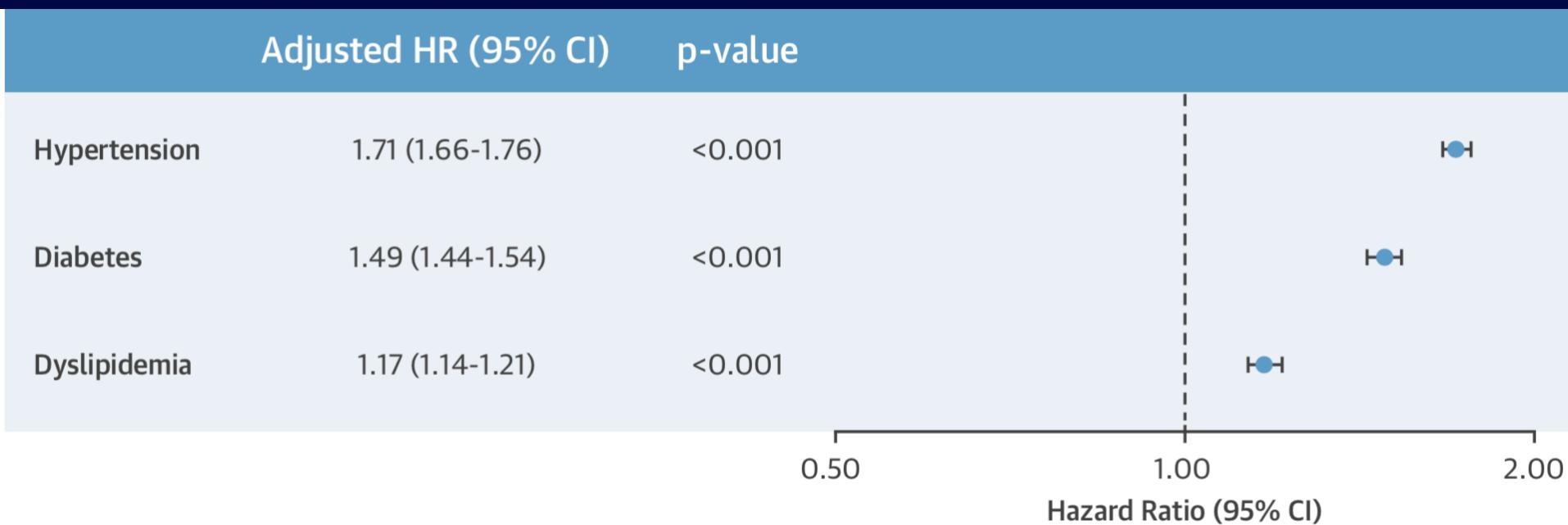
The CANHEART Aortic Stenosis Study

Andrew T. Yan, MD,^a Maria Koh, MSc,^b Kelvin K. Chan, MD, MSc,^c Helen Guo, MSc,^b David A. Alter, MD, PhD,^{b,d} Peter C. Austin, PhD,^b Jack V. Tu, MD, PhD,^{b,e} Harindra C. Wijeyasundera, MD, PhD,^{b,e} Dennis T. Ko, MD, MSc^{b,e}

- Studio di coorte osservazionale
- 1.120.000 soggetti > 65 anni con anamnesi CV negativa
- Follow-up mediano 13 anni

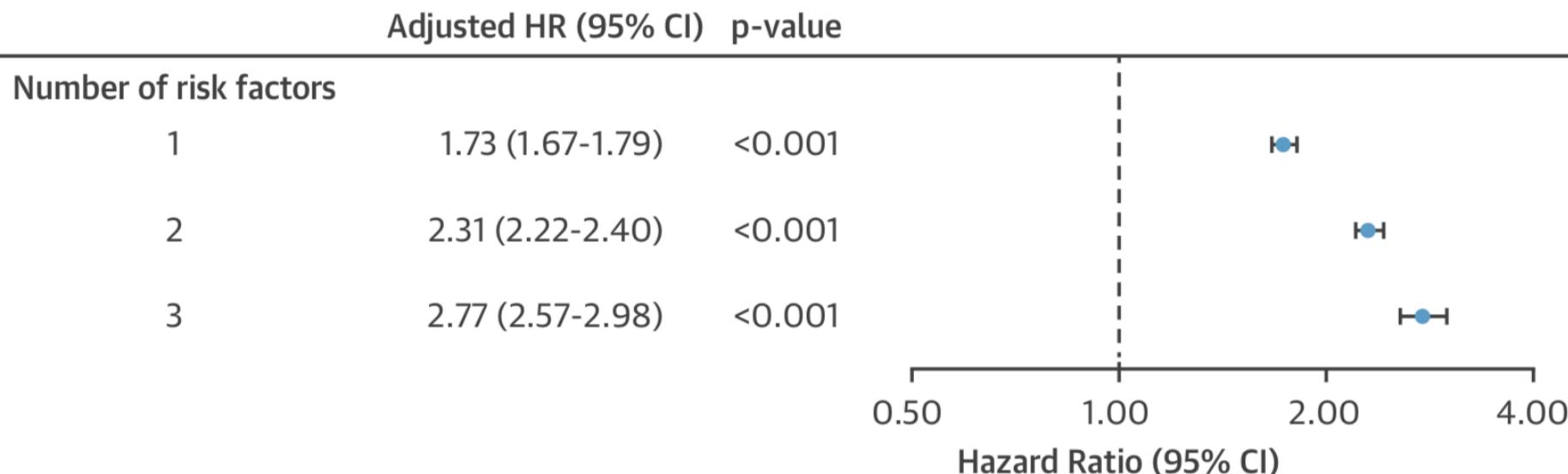
Outcome 1° : ospedalizzazione per SAO o intervento sulla valvola aortica

Relationship Between Cardiac RF and Aortic Stenosis



Yan AT et al, J Am Coll Cardiol 2017; 69:1523-32

Relationship Between Number of Cardiac Risk Factors and Aortic Stenosis



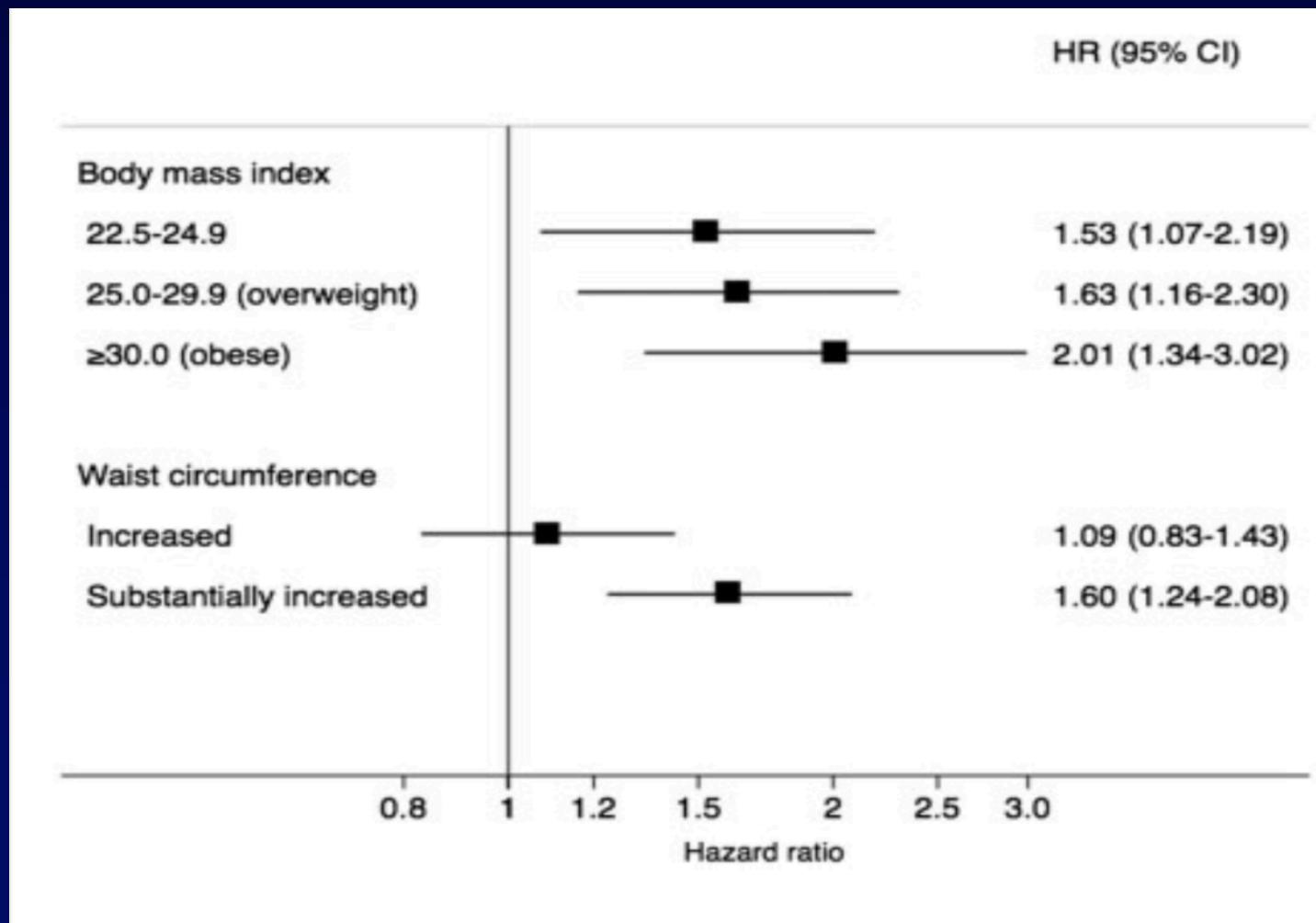
Yan AT et al, J Am Coll Cardiol 2017; 69:1523-32

Overall and abdominal obesity and incident aortic valve stenosis: two prospective cohort studies

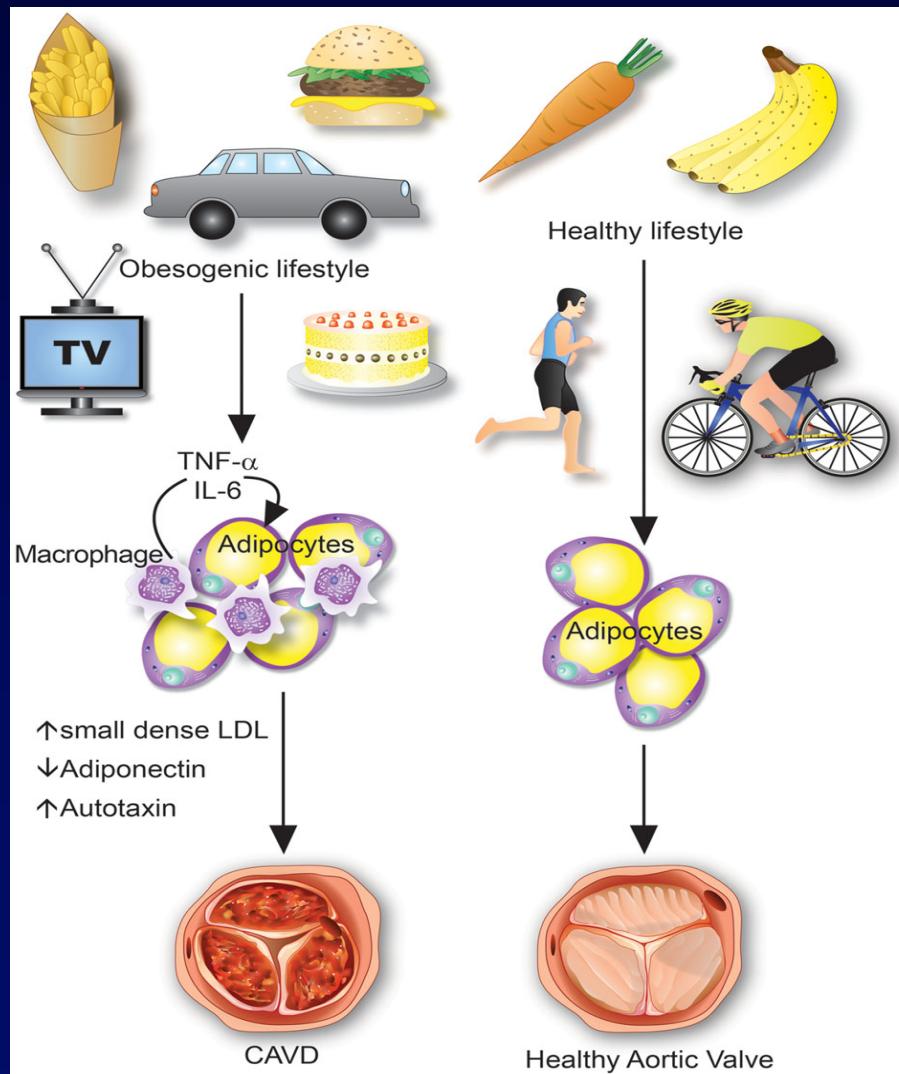
Susanna C. Larsson¹*, Alicja Wolk¹, Niclas Håkansson¹, and Magnus Bäck^{2,3}

- Studio di coorte osservazionale da database svedesi
- 71.817 soggetti con anamnesi CV negativa
- Follow-up mediano 15 anni

Association of BMI and WC With Risks of Aortic Valve Stenosis Requiring AVR



CAVD: Civilization Aortic Valve Disease



Mathieu and Arsenault, Eur Heart J 2017; 38:2190-200

Stenosi Aortica Degenerativa & Prevenzione

Agenda

- Meccanismi patogenetici
- Fattori di rischio predisponenti
- Interventi di prevenzione

Aortic Stenosis

Moving From Treatment to Prevention*

Brian R. Lindman, MD, MSc



- **Necessità di ampi studi di intervento che dimostrino nella realtà clinica efficacia e sicurezza del controllo dei FR CV in:**
 - **prevenzione della CAVS**
 - **effetto favorevole sulla prognosi**

Possible Ways to Prevent Aortic Valve Stenosis

Mayo Clinic Consumer Report Advice

- Taking steps to prevent rheumatic fever
- Addressing risk factors for CAD
- Taking care of your teeth and gums

1. Lipid - lowering therapy

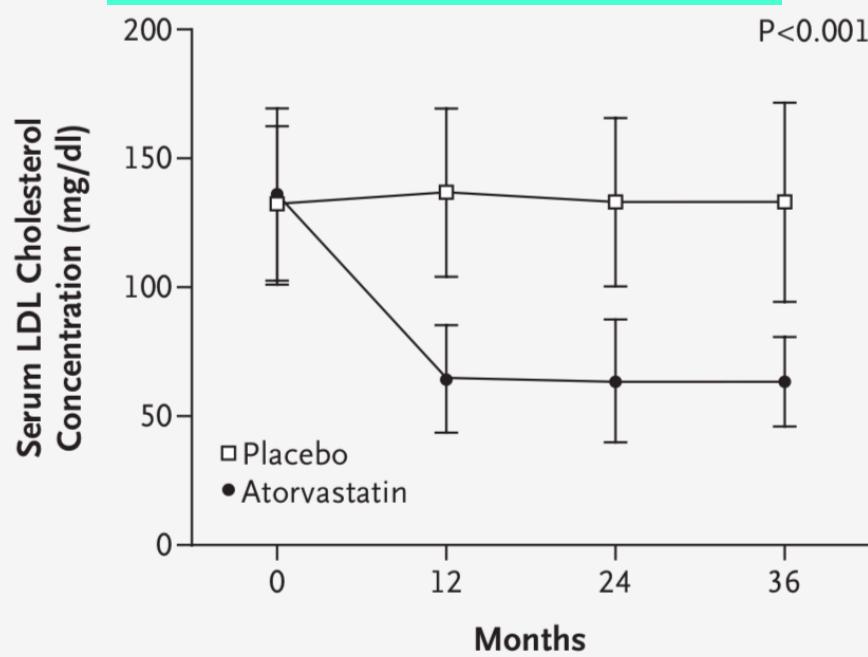
A Randomized Trial of Intensive Lipid-Lowering Therapy in Calcific Aortic Stenosis

S. Joanna Cowell, B.M., David E. Newby, M.D., Robin J. Prescott, Ph.D., Peter Bloomfield, M.D., John Reid, M.B., Ch.B., David B. Northridge, M.D., and Nicholas A. Boon, M.D., for the Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE) Investigators

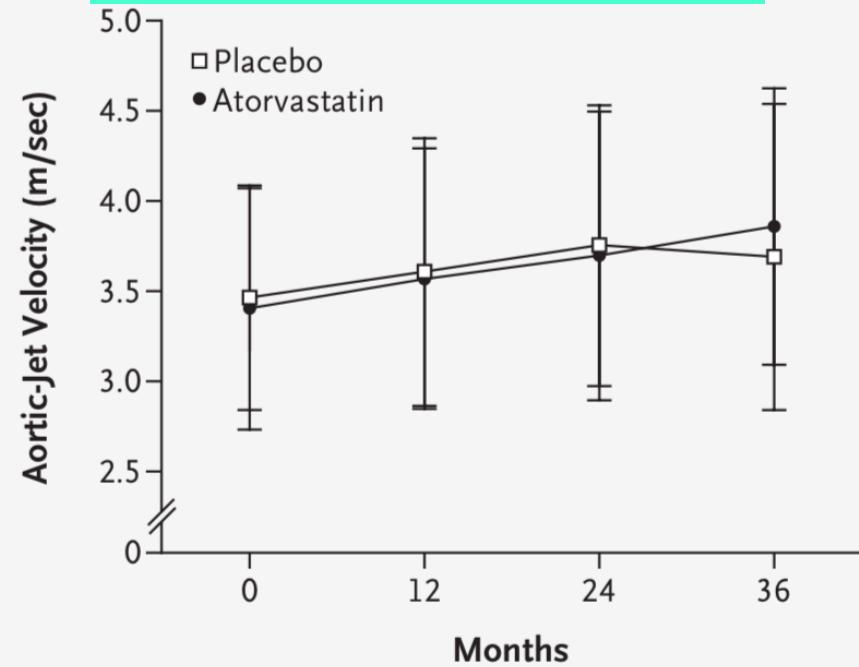
- 155 pazienti con SAO calcifica
- Randomizzati in doppio cieco ad ATORVASTATINA 80 mg o placebo
- Follow-up mediano 25 mesi

Variazioni colesterolo LDL e gradiente transvalvolare aortico

Variazione colesterolo LDL



Variazione gradiente trans-valvolare aortico



Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis

Anne B. Rossebø, M.D., Terje R. Pedersen, M.D., Ph.D.,
Kurt Boman, M.D., Ph.D., Philippe Brudi, M.D., John B. Chambers, M.D.,
Kenneth Egstrup, M.D., Ph.D., Eva Gerdts, M.D., Ph.D.,
Christa Gohlke-Bärwolf, M.D., Ingar Holme, Ph.D.,
Y. Antero Kesäniemi, M.D., Ph.D., William Malbecq, Ph.D.,
Christoph A. Nienaber, M.D., Ph.D., Simon Ray, M.D.,
Terje Skjærpe, M.D., Ph.D., Kristian Wachtell, M.D., Ph.D.,
and Ronnie Willenheimer, M.D., Ph.D., for the SEAS Investigators*

CONCLUSIONS

Simvastatin and ezetimibe did not reduce the composite outcome of combined aortic-valve events and ischemic events in patients with aortic stenosis. Such therapy reduced the incidence of ischemic cardiovascular events but not events related to aortic-valve stenosis. (ClinicalTrials.gov number, NCT00092677.)

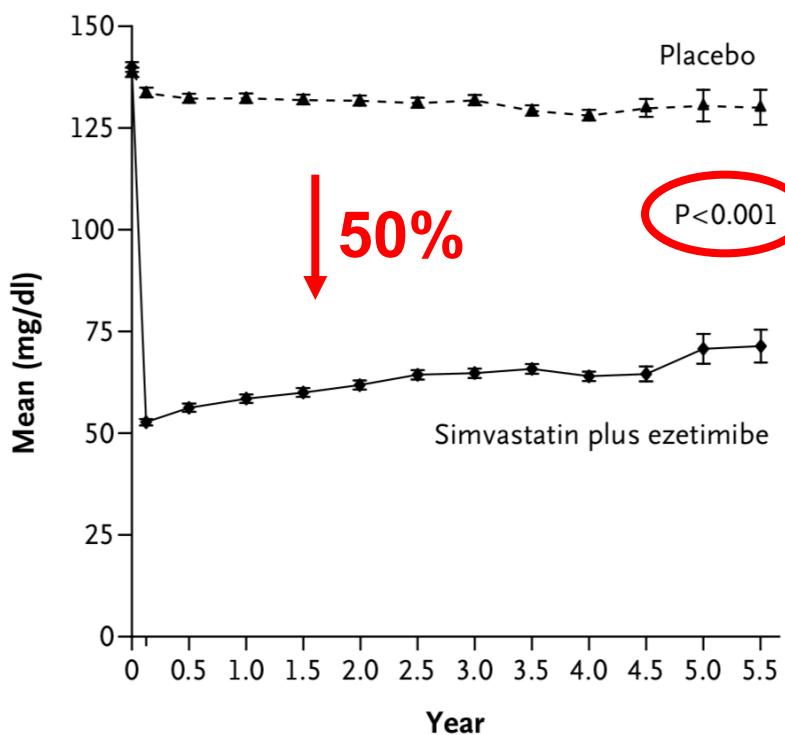
Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis

- 1873 pazienti asintomatici con SAO calcifica lieve - moderata
- Randomizzati in doppio cieco ad SIMVA 40 mg + EZETIMIBE 10 mg vs placebo
- Follow-up mediano 52 mesi
- Outcome 1° composito: eventi legati alla SAO + eventi ischemici

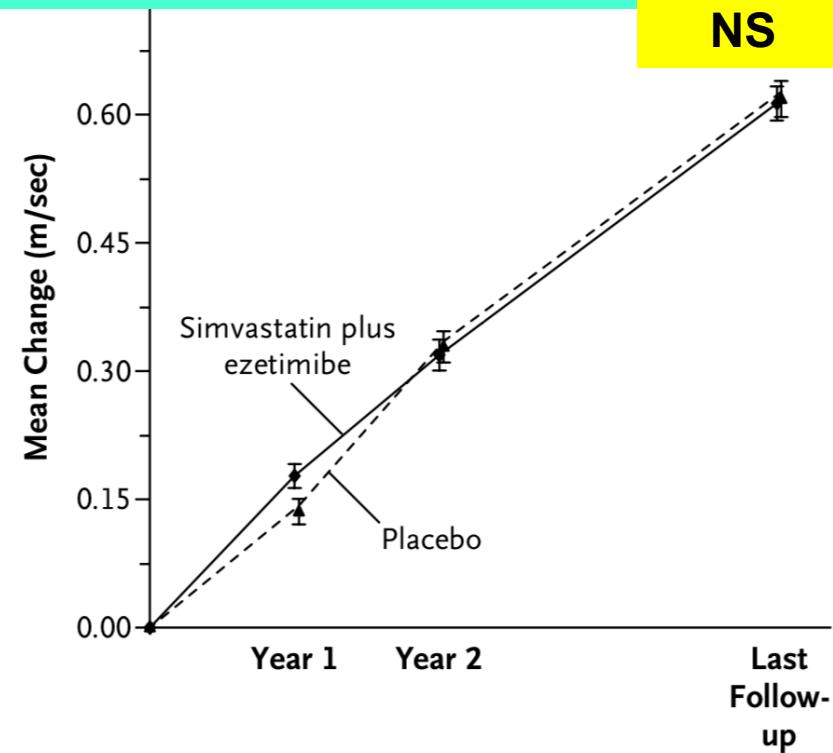
Rossebo AB et al, N Engl J Med 2008; 359:1343-56

Variazioni colesterolo LDL e gradiente transvalvolare aortico

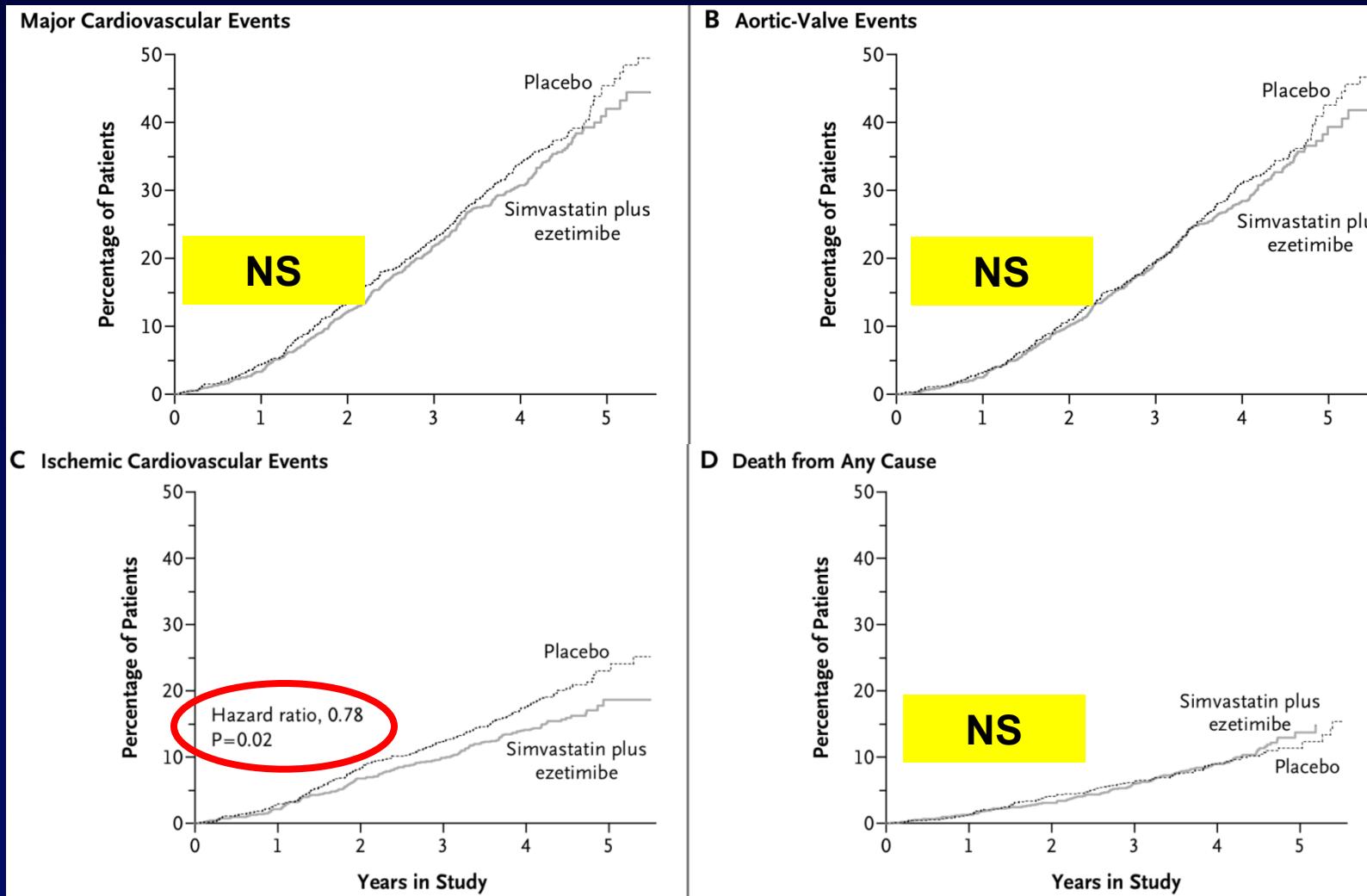
Variazione colesterolo LDL



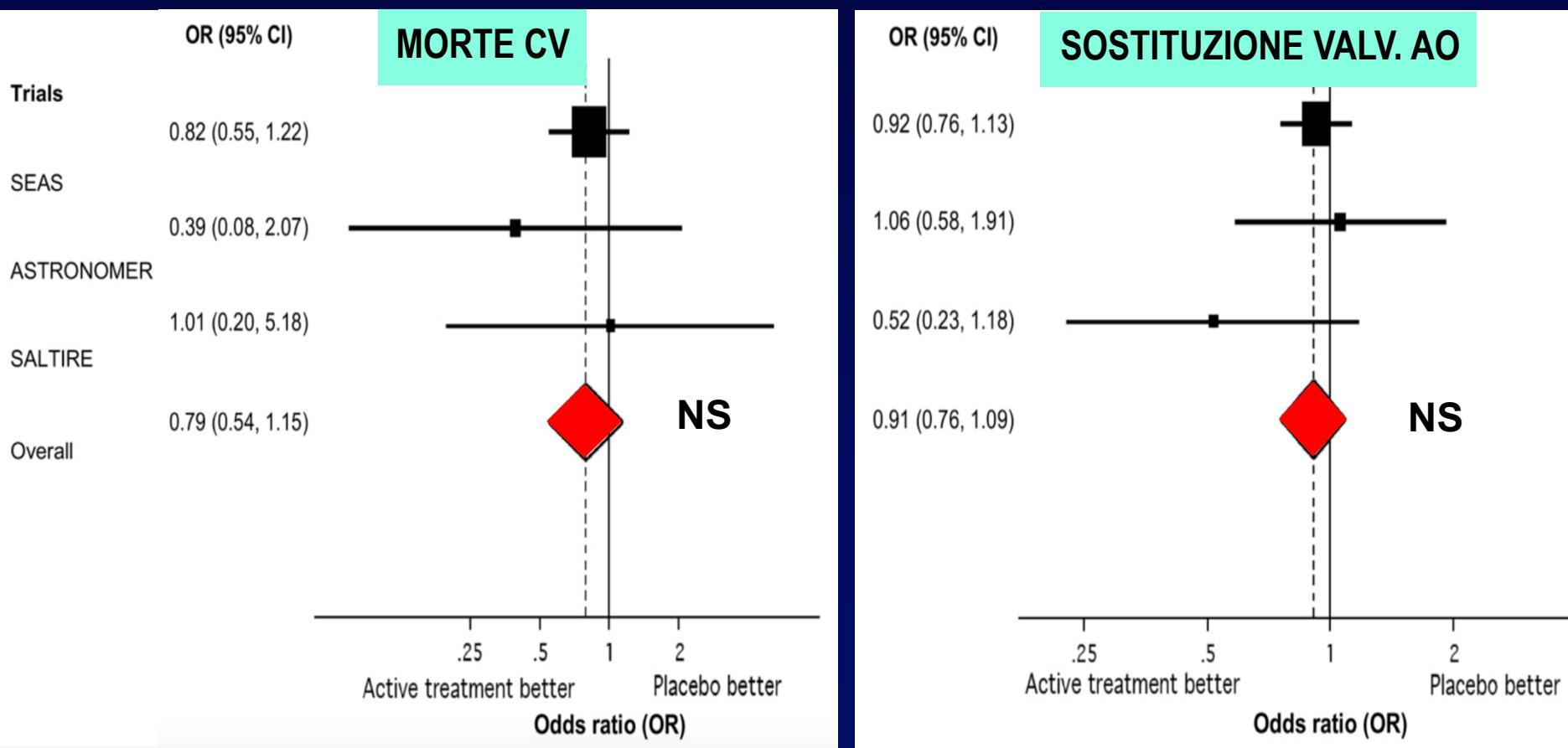
Variazione gradiente trans-valvolare aortico



Kaplan-Meier Curves for Primary and Secondary Outcomes and Death



Lipid Lowering on Progression of Mild to Moderate Aortic Stenosis: Meta-analysis of the Randomized Placebo-Controlled Clinical Trials on 2344 Patients



2. Calcium and phosphate lowering therapies



Check for updates

Full research paper

European Journal of

Preventive
Cardiology

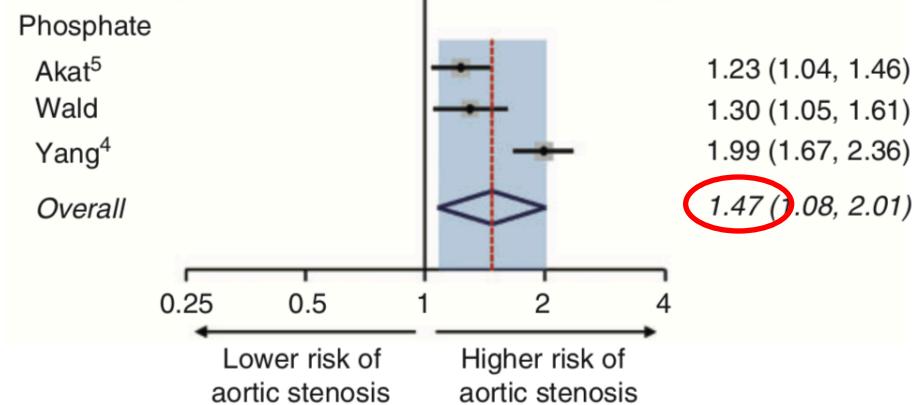
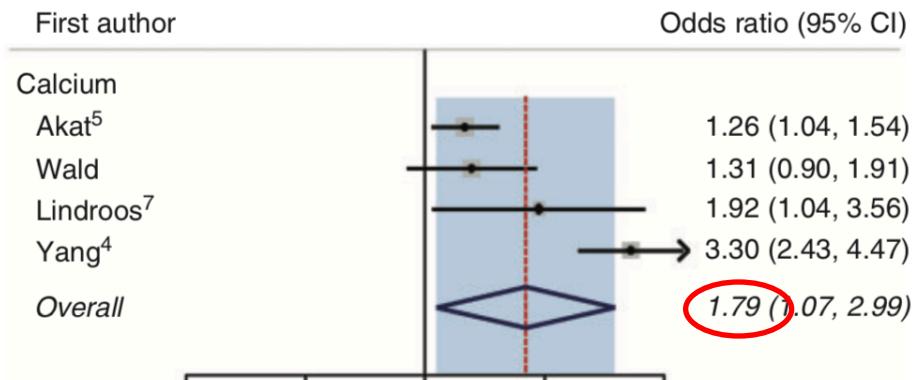
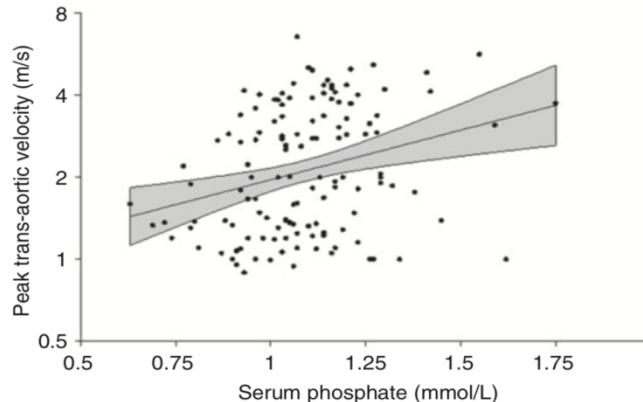
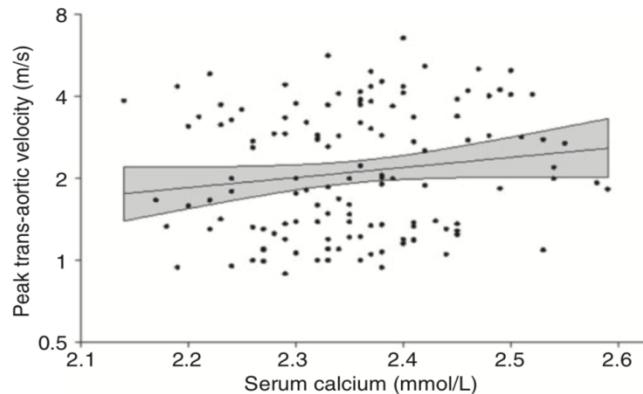


ESC

European Society
of Cardiology

Association between serum calcium, serum phosphate and aortic stenosis with implications for prevention

David S Wald and Jonathan P Bestwick



Research on the role of calcium metabolism in AS

Ongoing Studies

SALTIRE 2 Trial “Study Investigating the Effect of Drugs Used to Treat Osteoporosis on the Progression of Calcific Aortic Stenosis”

<https://clinicaltrials.gov/ct2/show/NCT02132026>

→ alendronate (or denosumab) vs placebo

Prevention of Aortic Stenosis (PAS) Pilot Trial

<https://doi.org/10.1186/ISRCTN17365679>

→ sevelamer (phosphate binding drug) vs placebo

Prevenzione SAO degenerativa

LG Valvulopatie ACC / AHA 2014

CLASS I

1. Hypertension in patients at risk for developing AS (stage A) and in patients with asymptomatic AS (stages B and C) should be treated according to standard GDMT, started at a low dose, and gradually titrated upward as needed with frequent clinical monitoring (51–53). (*Level of Evidence: B*)

CLASS III: No Benefit

1. Statin therapy is not indicated for prevention of hemodynamic progression of AS in patients with mild-to-moderate calcific valve disease (stages B to D) (54–56). (*Level of Evidence: A*)

Prevenzione SAO degenerativa

LG Valvulopatie ESC 2017

5.3 Medical therapy

No medical therapy for aortic stenosis can improve outcome compared with the natural history. Randomized trials have consistently shown that statins do not affect the progression of aortic stenosis.¹¹² Patients with symptoms of heart failure who are unsuitable candidates for surgery or TAVI or who are currently awaiting surgical or catheter intervention should be medically treated according to the heart failure guidelines.¹¹³ Coexisting hypertension should be treated. Medical treatment should be carefully titrated to avoid hypotension and patients should be re-evaluated frequently. Maintenance of sinus rhythm is important.

Take Home Messages (1)

- La prevalenza della SAO degenerativa dell'anziano è progressivamente aumentata negli ultimi decenni.
- Consegue ad un processo attivo con numerose analogie con l'aterosclerosi.
- Studi epidemiologici hanno individuato numerosi fattori di rischio per la SAO, in primo luogo ipercolesterolemia, ipertensione, sindrome metabolica e diabete mellito.
- I trial clinici randomizzati con statine ed ezetimibe hanno fallito nel ridurre la progressione della SAO degenerativa.

Take Home Messages (2)

- L'ipotesi di prevenire la SAO agendo sul metabolismo di calcio e fosforo è attraente ma non ancora sicuramente dimostrata.
- Al momento attuale il controllo dell'ipertensione e la prevenzione di sovrappeso e obesità costituiscono le uniche misure preventive.
- Gli studi futuri dovranno focalizzarsi sul trattamento delle lesioni aortiche in una fase più precoce del processo patogenetico.
- E' in corso la ricerca di marker molecolari circolanti per l'identificazione precoce di soggetti a rischio di sviluppare SAO calcifica, possibile target di terapie innovative.

