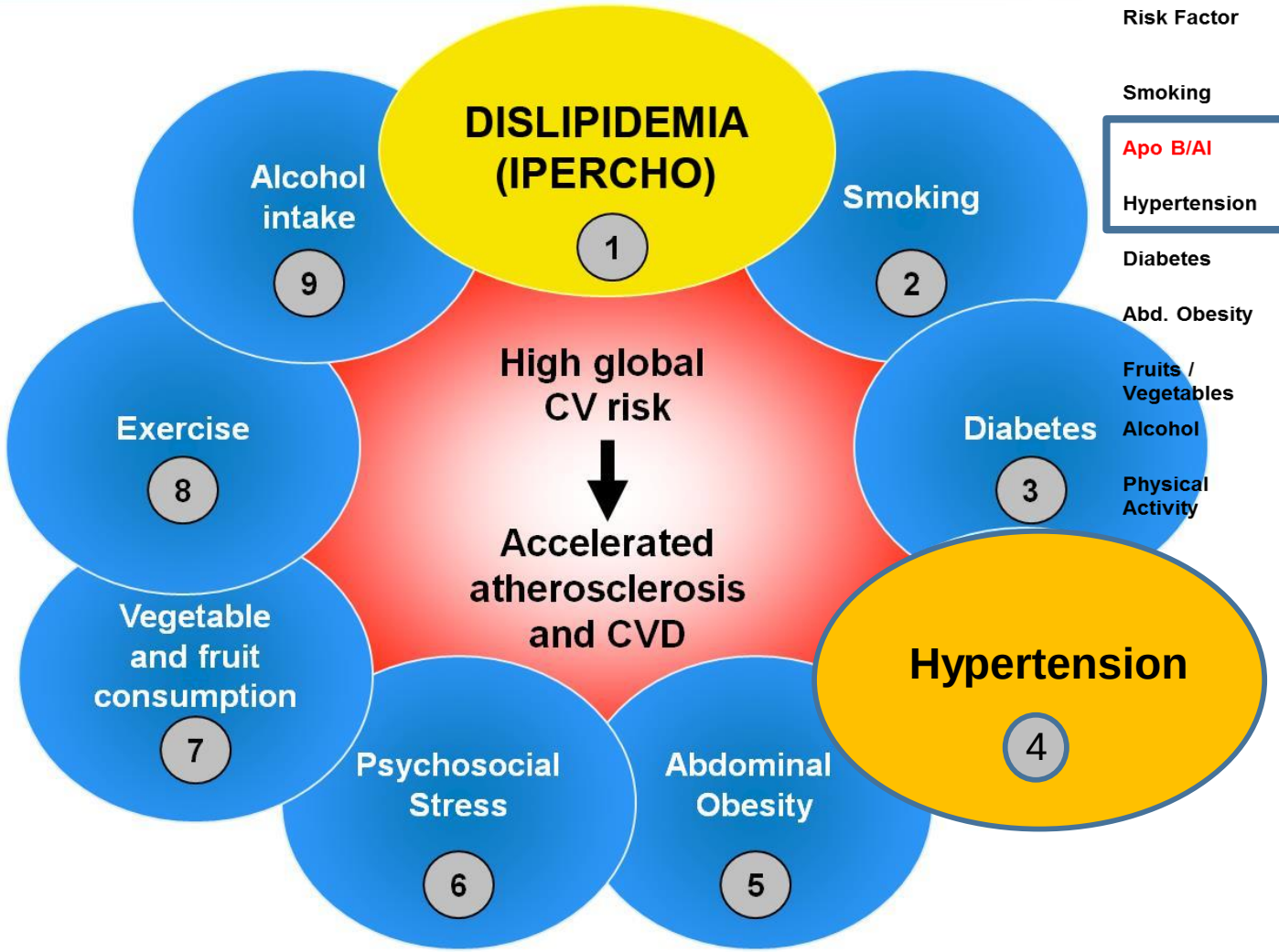

# Aderenza terapeutica: la sfida di gestire 2 fattori di rischio nello stesso paziente nell'era della polipillola

**Egidio Imbalzano, MD**
Dipartimento di Medicina Clinica e Sperimentale
Policlinico Universitario Messina

# Potentially Modifiable Risk Factors for Acute MI: The INTERHEART Study



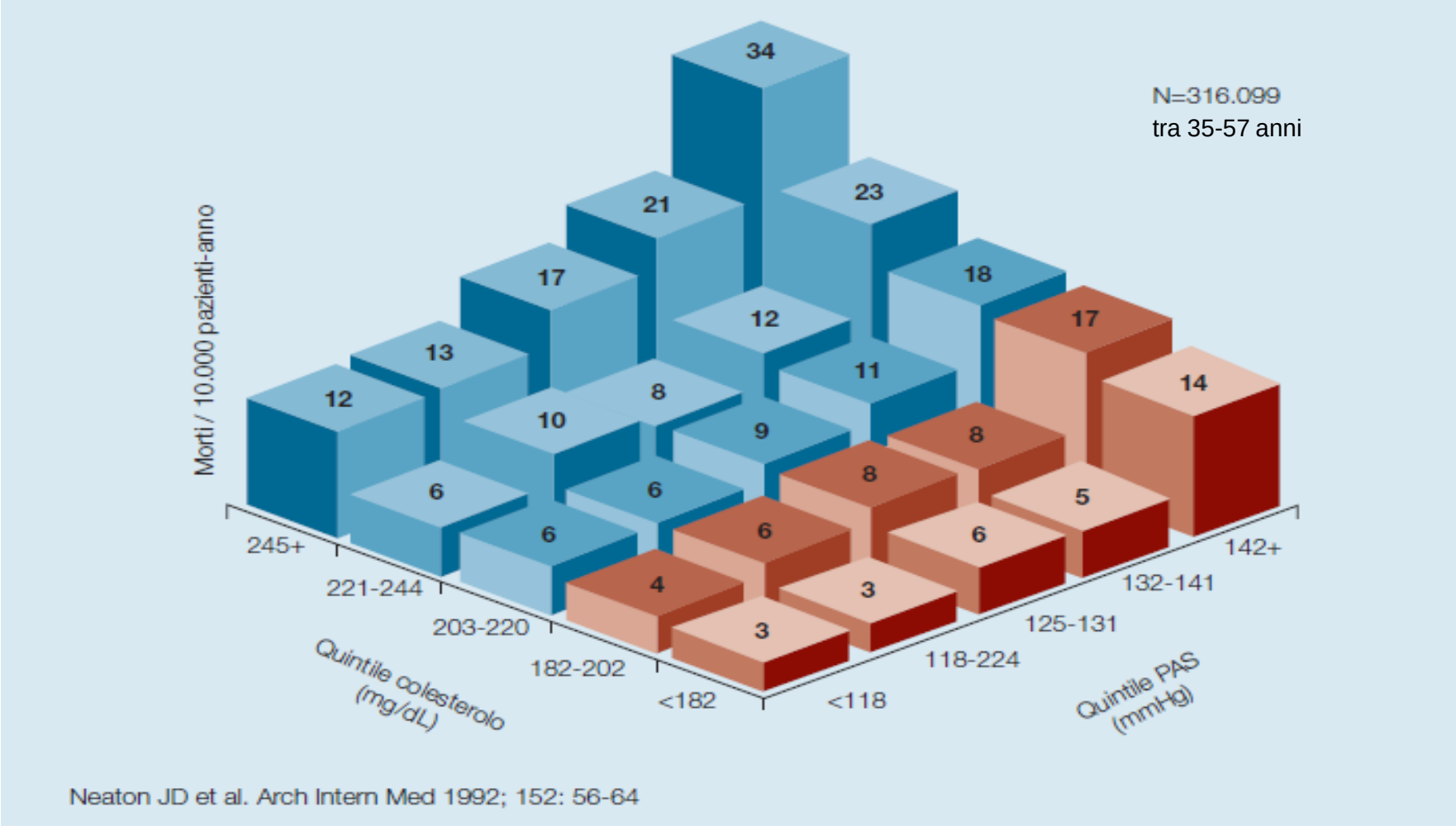

| Risk Factor | OR | Population Attributable Risk |
|---|---|---|
| Smoking | 2.87 | 35.7% |
| Apo B/AI | 3.25 | 49.2% |
| Hypertension | 1.91 | 17.9% |
| Diabetes | 2.37 | 9.9% |
| Abd. Obesity | 1.62 | 20.1% |
| Fruits / Vegetables | 0.70 | 13.7% |
| Alcohol | 0.91 | 6.7% |
| Physical Activity | 0.86 | 12.2% |

ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; MI, myocardial infarction.
Yusuf S, et al. Lancet 2004;364:937–52.

La combinazione di 9 fattori di rischio modificabili spiegherebbe oltre il 90% degli eventi CV!

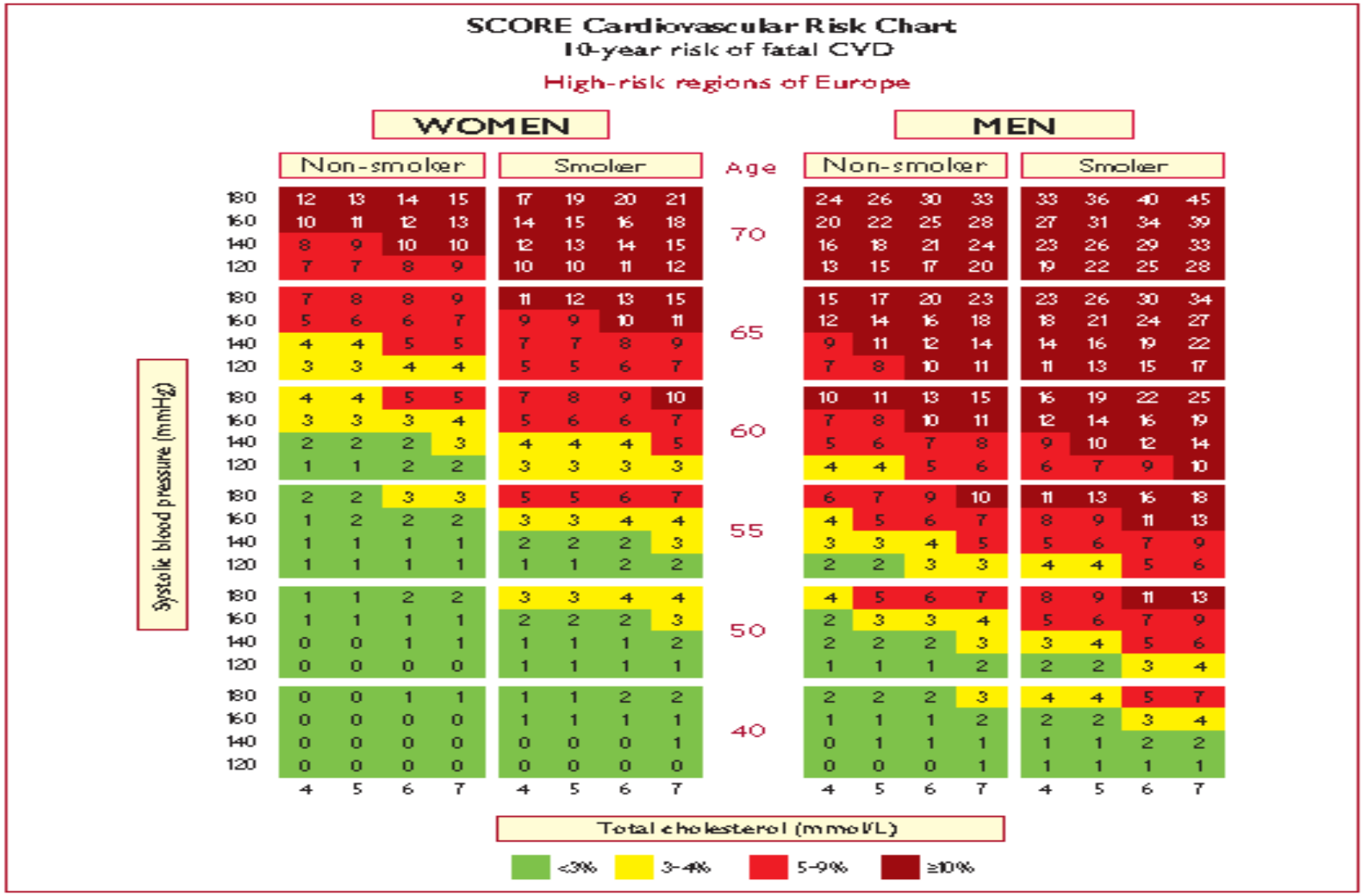
# Multiple Risk Factor Intervention Trial (MRFIT)

## Effetto additivo del colesterolo e della pressione arteriosa sul rischio di morte coronarica (CHD)




Neaton JD et al. Arch Intern Med 1992; 152: 56-64

Progressivi incrementi della colesterolemia e/o della pressione arteriosa si associano ad aumento del rischio di morte coronarica!




- Età
- Sesso
- Fumo
- PAS
- Col totale

2019 ESC/EAS Guidelines for themanagement of dyslipidaemias: lipid modification to reduce cardiovascular risk

# Possibile role of Hypercholesterolemia in the pathogenesis of Hypertension

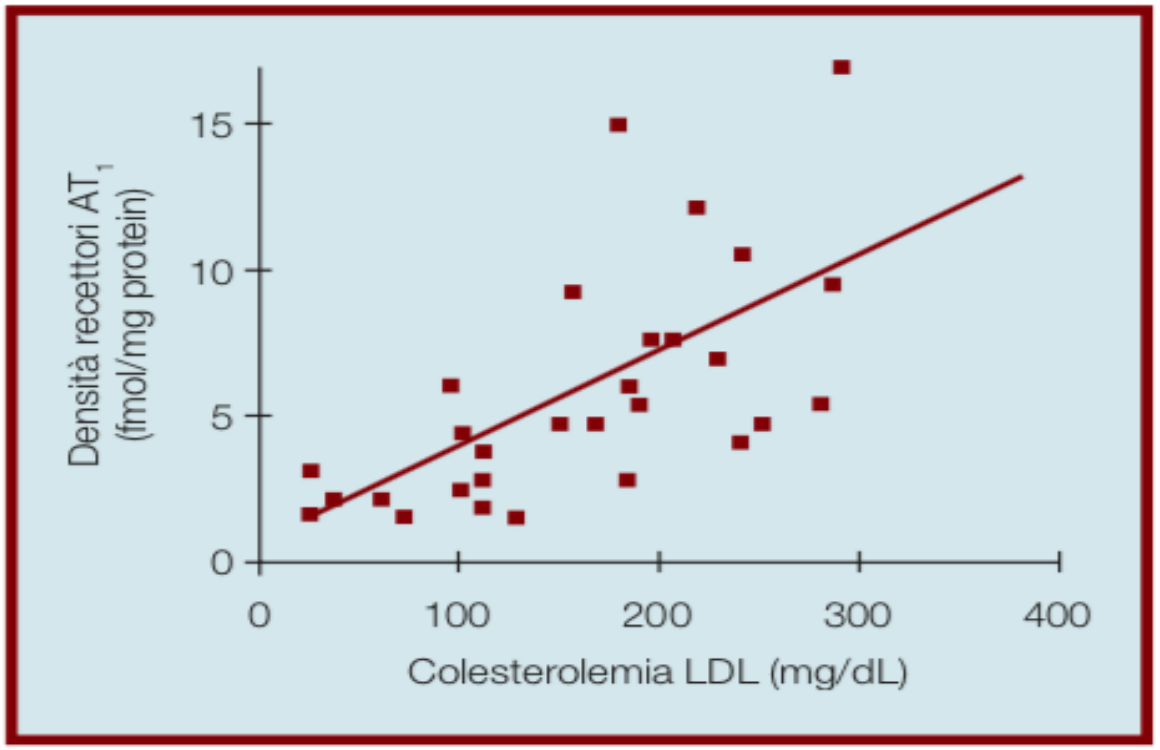



**FIGURA 4** Correlazione lineare tra livelli plasmatici di colesterolo LDL e densità di recettori AT1 per la angiotensina II a livello piastrinico.

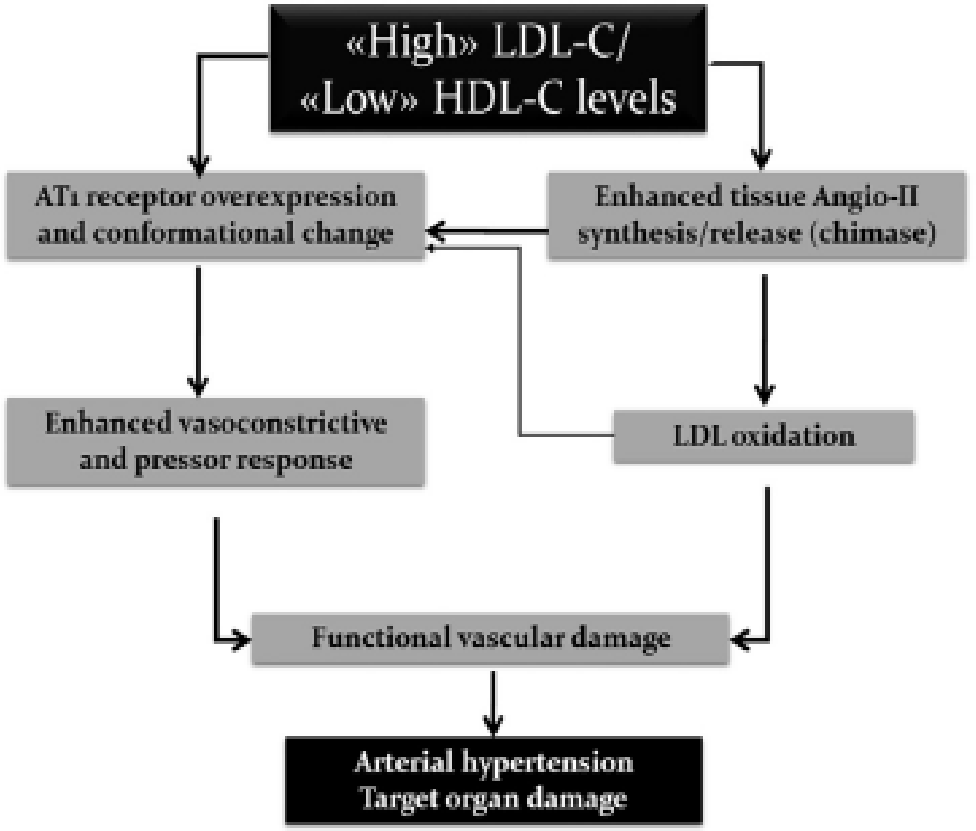



**Figure 2** Possible role of hypercholesterolemia in the pathogenesis of hypertension.

Review

# Renin—angiotensin system at the crossroad of hypertension and hypercholesterolemia

**Abstract** *Aim:* The aim of this study is to discuss the reliable scientific evidence of an interactive link between hypertension and hypercholesterolemia considering the metabolic pathways and the pathogenetic mechanisms connecting the two risk factors.
*Data synthesis:* Hypertension and hypercholesterolemia are highly prevalent in the general population and their coexistence in the same subjects additively increases the risk of cardiovascular disease. Probably, hypercholesterolemia is also a risk factor for the development of hypertension. On the other side, it is also possible that lipid-lowering treatment could improve blood pressure control. Although the mechanisms of interaction between these two risk factors have not been completely elucidated thus far, there is rapidly growing evidence that the involvement of the renin—angiotensin system (RAS) can be considered as the common link between hypertension and hypercholesterolemia. In particular, hypercholesterolemia seems to promote the upregulation of type 1 angiotensin II (AT1) receptor genes because of an increase in the stability of mRNA followed by structural overexpression of vascular AT1 receptors for angiotensin II. The treatment of both risk factors greatly improves individual risk profile, especially when statins and RAS blockers are used together.
*Conclusions:* Hypertension and hypercholesterolemia are highly coprevalent and strongly related from a pathophysiological point of view. The RAS could be the main mediator of this link.

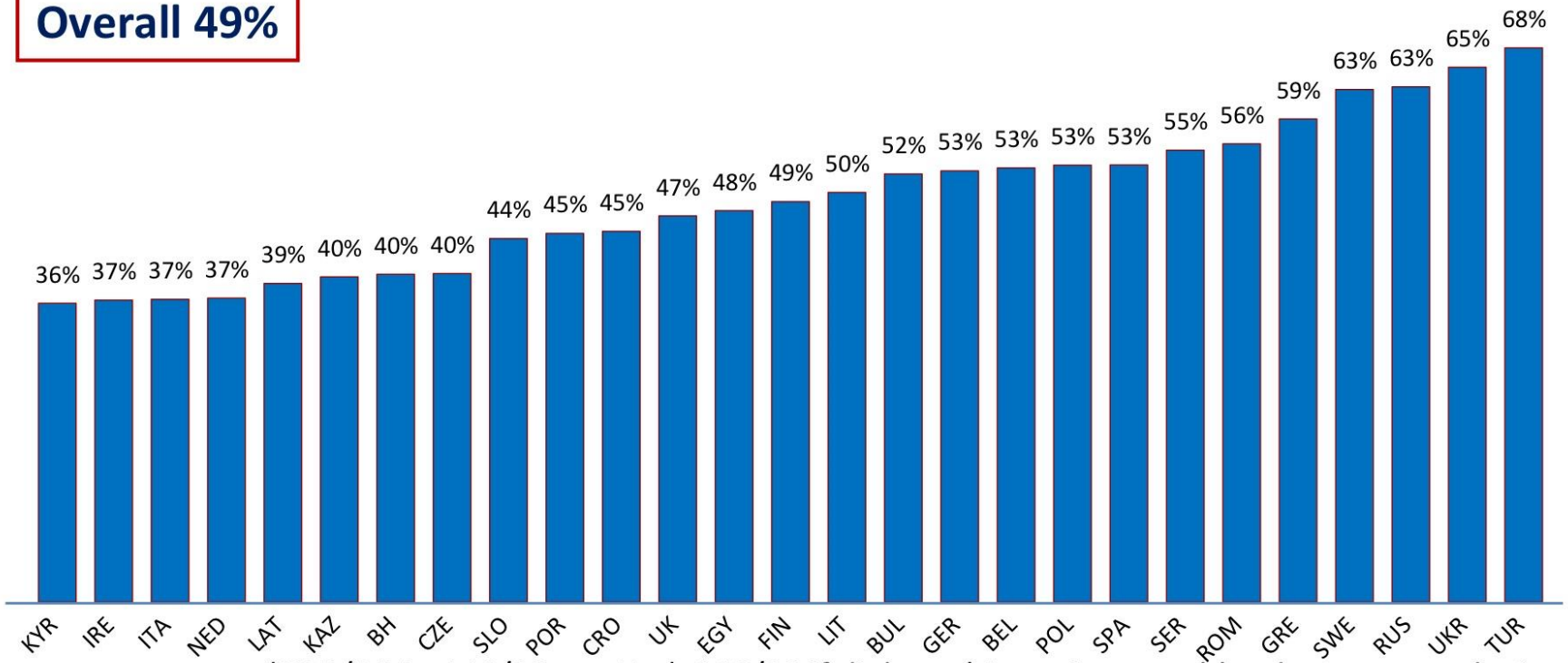
Borghi et al. Nutrition, Metabolism & Cardiovascular Diseases (2017) 27, 115-120

# 51% of patients with uncontrolled BP (>140/90 mmHg)



## Hypertension
### Therapeutic control*

**Overall 49%**

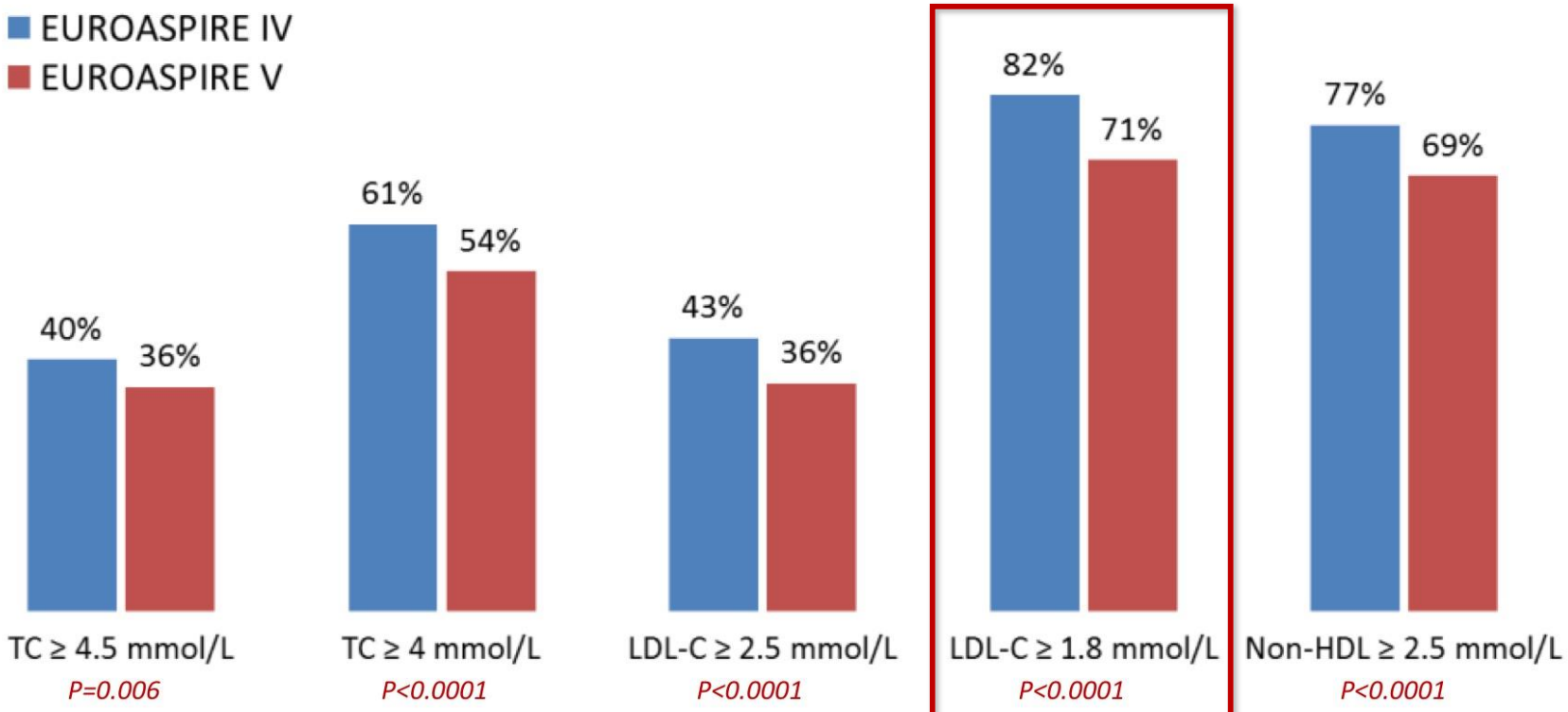



*SBP/DBP <140/90 mmHg (<140/80 if diabetes) in patients on blood pressure reducing drugs; Standardized for age and gender

# 71% of patients with uncontrolled LDL-C (≥1.8 mmol/L)

ESC Congress Munich 2018
25-29 August
Where the world of cardiology comes together

## Prevalence of raised lipid levels
### EUROASPIRE V vs IV




ESC Congress Munich 2018

IV (2012-2015) e V (2016-2018)

# Corretta terapia farmacologica

Una corretta Terapia Farmacologica (es. antipertensivi, statine, antiaggreganti) porta alla riduzione[1] del
**50% della mortalità per MCV**

**Il 70% dei pazienti necessitano di**
**2 o più farmaci per raggiungere il target**

**4 pazienti su 10**
**non continuano il trattamento farmacologico prescritto**

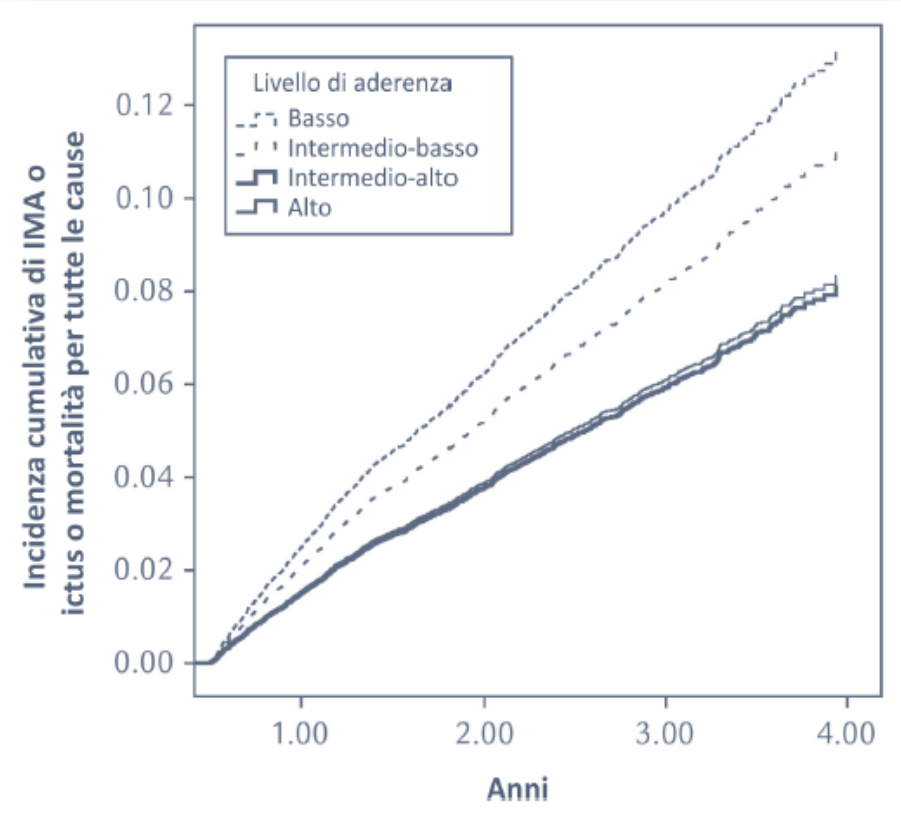
Il numero delle compresse assunte è inversamente proporzionale all'aderenza al trattamento

*Volpe M et al. Il ruolo dell'aderenza alla trattamento farmacologico nella terapia cronice delle malattie cardiovascolari: documento intersocietario di consenso. G Ital Cardiol 2014;15(10 Suppl 1): 3S-10S; Bangalore S. Fixed-Dose Combinations Improve Medication Compliance: A Meta-Analysis; Blaschke et al., 2012*

# IL PROBLEMA DELL'ADERENZA

- La scarsa aderenza ai farmaci è associata a conseguenze negative sulla salute:
- **in primo luogo**, ne deriva uno scarso controllo dei fattori di rischio ed in particolare dei valori pressori e del colesterolo
- **in secondo luogo**, sottovalutare la scarsa aderenza può tradursi in un'inutile intensificazione del trattamento con la potenziale comparsa di effetti avversi e l'innesco di un "circolo vizioso" che di fatto può esacerbare la mancata aderenza

# Il ruolo dell'aderenza al trattamento farmacologico nella terapia cronica delle malattie cardiovascolari




**La mortalità e gli eventi CV** maggiori **aumentano** nei pazienti con **scarsa aderenza** alla terapia

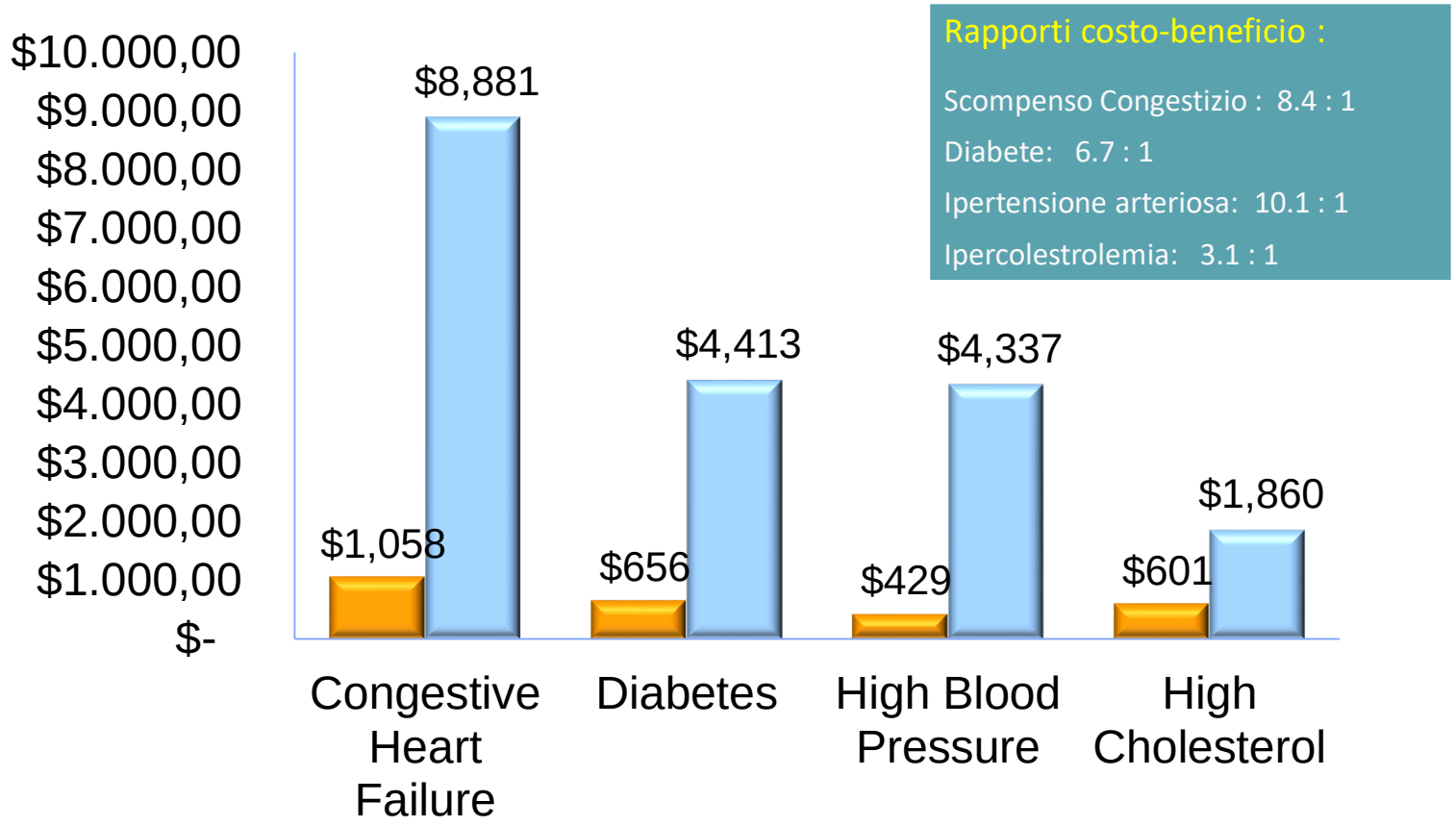
La **scarsa aderenza** nei pazienti affetti da patologie Cardiovascolari causa circa

**200,000 morti l'anno**

La **scarsa aderenza** si stima che costi **125 miliardi euro/anno**

*G Ital Cardiol 2014;15(Suppl 1):3S-10S*

# L'aumento dell'aderenza aumenta la spesa farmaceutica, ma riduce i ricoveri ospedalieri e le spese sanitarie globali




**Rapporti costo-beneficio :**

Scompenso Congestizio : 8.4 : 1

Diabete: 6.7 : 1

Ipertensione arteriosa: 10.1 : 1

Ipercolestrolemia: 3.1 : 1

Roebuck MC, et al. Health Affairs 2011;30(1):91-99.

# Aderenza entra fortemente come aspetto da considerare nelle nuove LG

**FOCUS sul tema dell'ADERENZA**:

Importanza della valutazione dell'aderenza al trattamento, la causa maggiore di scarso controllo dei valori pressori.

Ruolo chiave di infermieri e farmacisti per il supporto, educazione e monitoraggio dei pazienti ipertesi

**SINGLE PILL COMBINATION (SPC)**

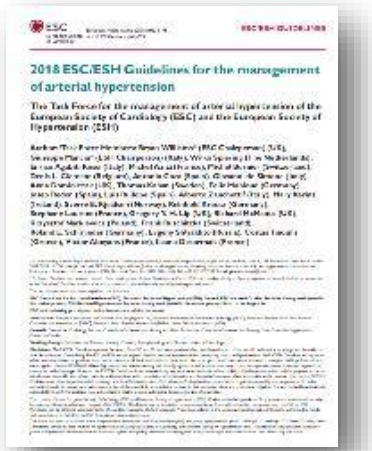
sono ora raccomandate in gran parte degli ipertesi come terapia iniziale

**EFFICACIA**

**TOLLERABILITÀ**

**SEMPLICITÀ**

Il paziente preferisce assumere 1 compressa




*Williams B. et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. European Heart Journal (2018) 00, 1–98 doi:10.1093/eurheartj/ehy339*

ESC European Society of Cardiology
European Heart Journal (2018) 00, 1–98
doi:10.1093/eurheartj/ehy339
ESC/ESH GUIDELINES

# 2018 ESC/ESH Guidelines for the management of arterial hypertension

## Strategia di trattamento farmacologico antipertensivo

| Raccomandazioni | Classe[a] | Livello[b] |
|---|---|---|
| Fra tutti i farmaci antipertensivi, gli ACE-inibitori, gli ARB, i betabloccanti, i calcioantagonisti ed i diuretici (tiazidici e simil-tiazidici come il clortalidone e l'indapamide) si sono dimostrati efficaci nel ridurre i valori pressori e l'incidenza di eventi CV nei RCT e, pertanto, sono indicati quale strategia primaria di trattamento antipertensivo[2] | I | A |
| Per la maggior parte dei pazienti ipertesi si raccomanda inizialmente di instaurare una terapia di associazione, prediligendo la combinazione di un bloccante del SRA (ACE-inibitore o ARB) con un calcioantagonista o un diuretico, ma possono essere utilizzate altre combinazioni delle cinque principali classi di farmaci[233,318,327,329,341-345]. | I | A |
| Si raccomanda di associare i betabloccanti con una delle altre principali classi di farmaci in caso di indicazioni specifiche al loro utilizzo, es. in presenza di angina, nei pazienti post-infartuati o con scompenso cardiaco, o per il controllo della frequenza cardiaca[300,341]. | I | A |
| Si raccomanda di iniziare il trattamento antipertensivo con una associazione di due farmaci, preferibilmente con SPC, fatta eccezione per i pazienti anziani e fragili e per quelli a basso rischio con ipertensione di grado 1 (specie in presenza di PAS <150 mmHg)[342,346,351]. | I | B |
| Qualora la terapia di associazione con due farmaci sia inefficace nel conseguire il controllo pressorio[c], si raccomanda di intensificare il trattamento passando ad una triplice combinazione costituita generalmente da un bloccante del SRA associato a un calcioantagonista e un diuretico tiazidico o simil-tiazidico, preferibilmente come SPC[349,350]. | I | A |
| Qualora la triplice combinazione sia inefficace nel conseguire il controllo pressorio[c], si raccomanda di intensificare il trattamento aggiungendo lo spironolattone o, in caso di intolleranza, un altro diuretico come l'amiloride o un altro diuretico ad alte dosi, un betabloccante o un alfabloccante[310]. | I | B |
| Non è raccomandata l'associazione di due bloccanti del SRA[291,298,299]. | III | A |

*Williams B. et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. European Heart Journal (2018) 00, 1–98 doi:10.1093/eurheartj/ehy339*

ESC European Society of Cardiology European Heart Journal (2018) 00, 1–98 doi:10.1093/eurheartj/ehy339
ESC/ESH GUIDELINES
2018 ESC/ESH Guidelines for the management of arterial hypertension

# Statins

**Managing cardiovascular disease risk in hypertensive patients beyond BP: statins.** For hypertensive patients at moderate CVD risk or higher, or those with established CVD, BP lowering alone will not optimally reduce their risk. These patients would also benefit from statin therapy, which further reduces the risk of a myocardial infarction by approximately one-third and stroke by approximately one-quarter, even when BP is controlled. Similar benefits have been seen in hypertensive patients at the border between low and moderate-risk. Thus, many more hypertensive patients would benefit from statin therapy than are currently receiving this treatment.

**Treatment of CV risk factors associated with hypertension**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| CV risk assessment with the SCORE system is recommended for hypertensive patients who are not already at high or very high risk due to established CVD, renal disease, or diabetes.[33] | I | B |
| For patients at very high CV risk, statins are recommended to achieve LDL-C levels of <1.8 mmol/L (70 mg/dL), or a reduction of ≥50% if the baseline LDL-C is 1.8–3.5 mmol/L (70–135 mg/dL).[596,599,602] | I | B |
| For patients at high CV risk, statins are recommended to achieve an LDL-C goal of <2.6 mmol/L (100 mg/dL), or a reduction of ≥50% if the baseline LDL-C is 2.6–5.2 mmol/L (100–200 mg/dL).[599,602] | I | B |
| For patients at low–moderate CV risk, statins should be considered to achieve an LDL-C value of <3.0 mmol/L (115 mg/dL).[598] | IIa | C |
| Antiplatelet therapy, in particular low-dose aspirin, is recommended for secondary prevention in hypertensive patients.[35,604] | I | A |
| Aspirin is not recommended for primary prevention in hypertensive patients without CVD.[35,604] | III | A |

ESC European Society of Cardiology
European Heart Journal (2018) 00, 1–98
doi:10.1093/eurheartj/ehy339
ESC/ESH GUIDELINES
2018 ESC/ESH Guidelines for the management of arterial hypertension

# Polypills – the new treatment strategy



Polypills have also emerged as SPCs (i.e. a fixed-dose combination of one or more antihypertensive agents with a statin and low-dose aspirin), with the rationale that hypertensive patients are often at sufficient CV risk to benefit from statin therapy. Studies of bioequivalence suggest that when combined in the polypill, different agents maintain all or most of their expected effect.[355] Furthermore, studies performed in the setting of secondary prevention, particularly in patients with a previous myocardial infarction, have shown that use of the polypill is accompanied by a better adherence to treatment compared with separate medications.[356] The ESC Guidelines for the management of myocardial infarction have recommended polypill use to improve long-term adherence to prescribed therapy (class IIa, level

THE LANCET
Volume 389 · Number 10073 · Pages 983–1074 · March 11–17, 2017
www.thelancet.com

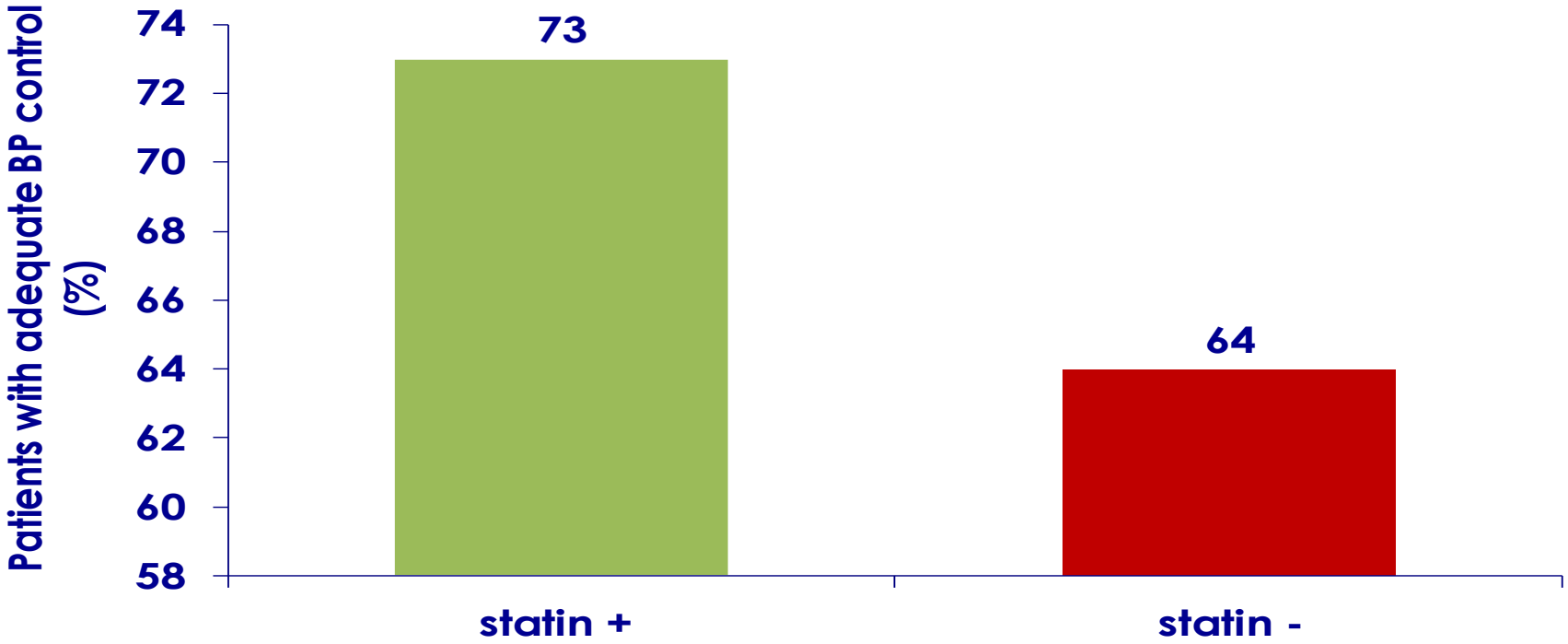
"Although not a cure for the worldwide epidemic of atherosclerosis, polypill therapy is one of the most scalable strategies to reduce the risk of premature mortality from non-communicable diseases, including atherosclerosis, by 25% by 2025 by improving drug adherence and access."

See Series page 1055

# Studio PERSPECTIVA

587 patients with concomitant hypertension and hypercholesterolemia (mean age 56.7 years) single-pill combination perindopril/amlodipine at a dose of 5/5, 10/5 or 10/10 mg/day.
226 treated with statin (statin [+] group)

60 days follow-up

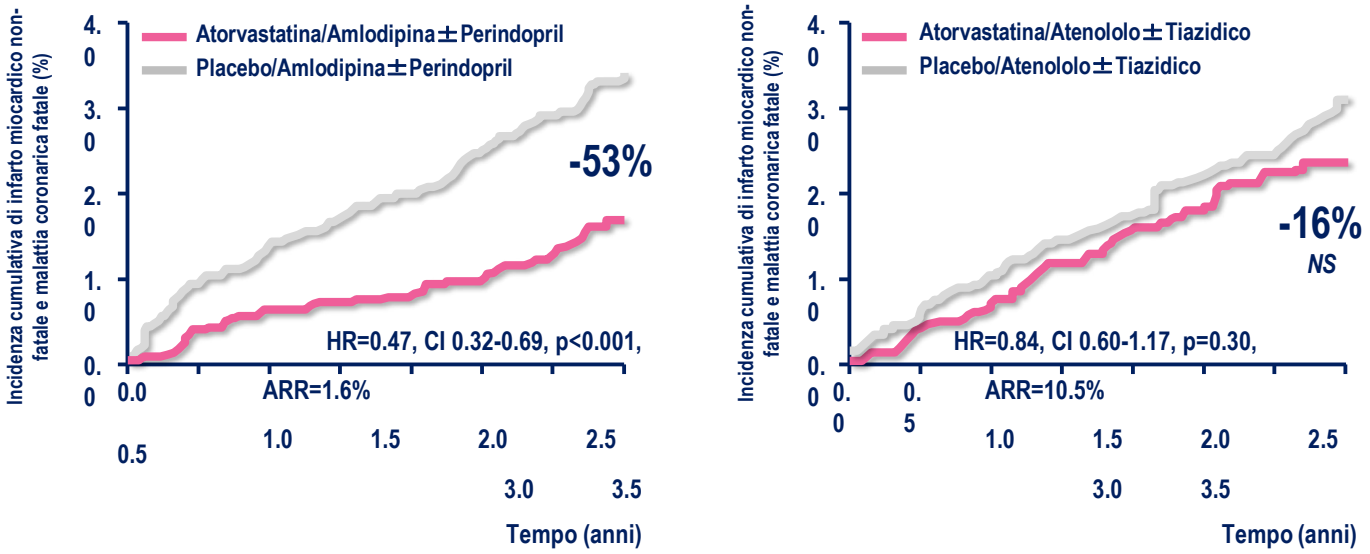



High Blood Pressure & Cardiovascular Prevention 2017, 24: 85–93

# Sinergia tra atorvastatina, amlodipina e perindopril per la protezione CV

***ASCOT-LLA, RCT***

*n= 10,305 pazienti ipertesi con almeno 3 fattori di rischio CV e colesterolo totale ≤6.5 mmol/L. Follow-up 3.3 anni.*




*"The more likely basis for the proposed synergy is supported by the observation that significant benefits of atorvastatin were seen in the amlodipine/perindopril–based treatment limb within 3 months of assignment to treatment"*

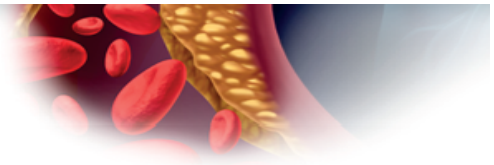
Sever et al. *Eur Heart J.* 2006;27:2982-2988.

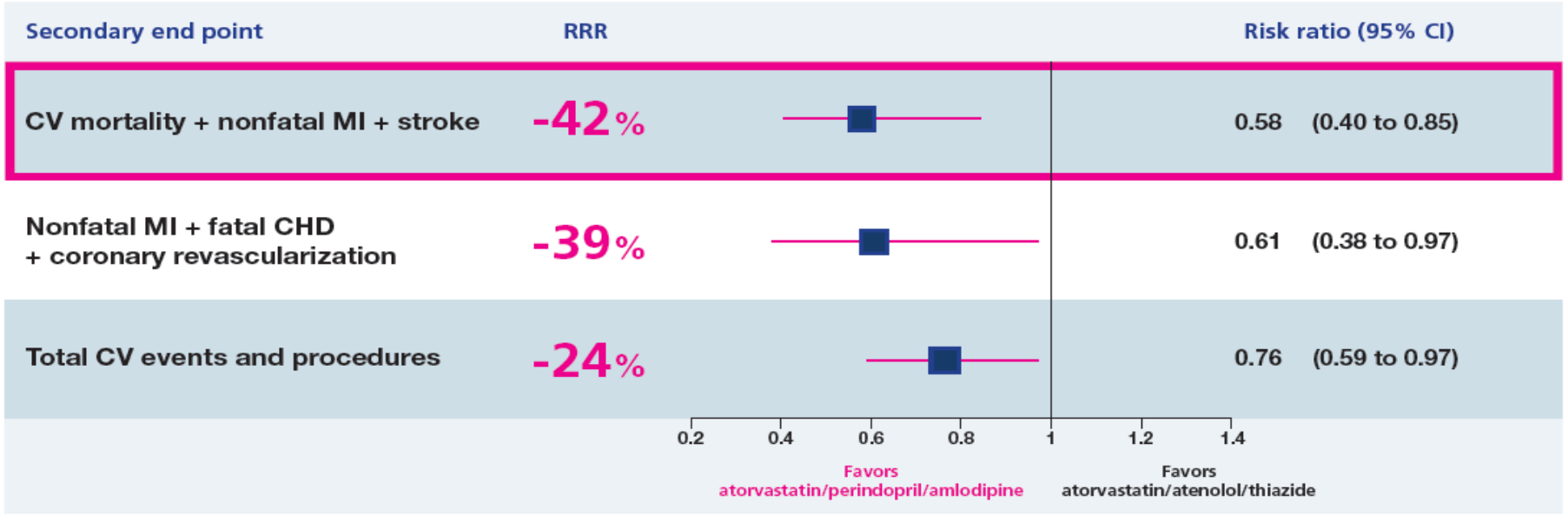
# Studio ASCOT

## Analisi in pazienti trattati con due diversi regimi di triplice combinazione per 3.3 anni

Anglo-Scandinavian ascot Cardiac Outcomes Trial

SUBANALYSIS 2016






ASCOT-LLA patients (either untreated or treated hypertension, with a fasting cholesterol of 6.5 mmol/L (250 mg/dL) or lower, not currently taking a statin or a fibrate, and with at least three risk factors for cardiovascular disease) were randomized to either 10 mg atorvastatin daily or the matching placebo.
On-treatment analysis in 3792 patients receiving atorvastatin + perindopril + amlodipine at every visit (1814 patients) versus atorvastatin + atenolol + bendroflumethiazide at every visit (1978 patients) over 3.3 years in an analysis of the ASCOT-LLA trial.
Primary end point in the ASCOT-LLA trial: 38% decrease [0.62 (0.36-1.08)] of the composite of non-fatal myocardial infarction and fatal coronary heart diseases.
CHD: coronary heart disease, CV: cardiovascular, MI: myocardial infarction, RRR: relative risk reduction, CI: confidence interval.
*The efficacy has been demonstrated with mono-components taken separately.


1. Bertrand M, et al. *Am J Cardiovasc Drugs*. 2016;16(4):241-253.

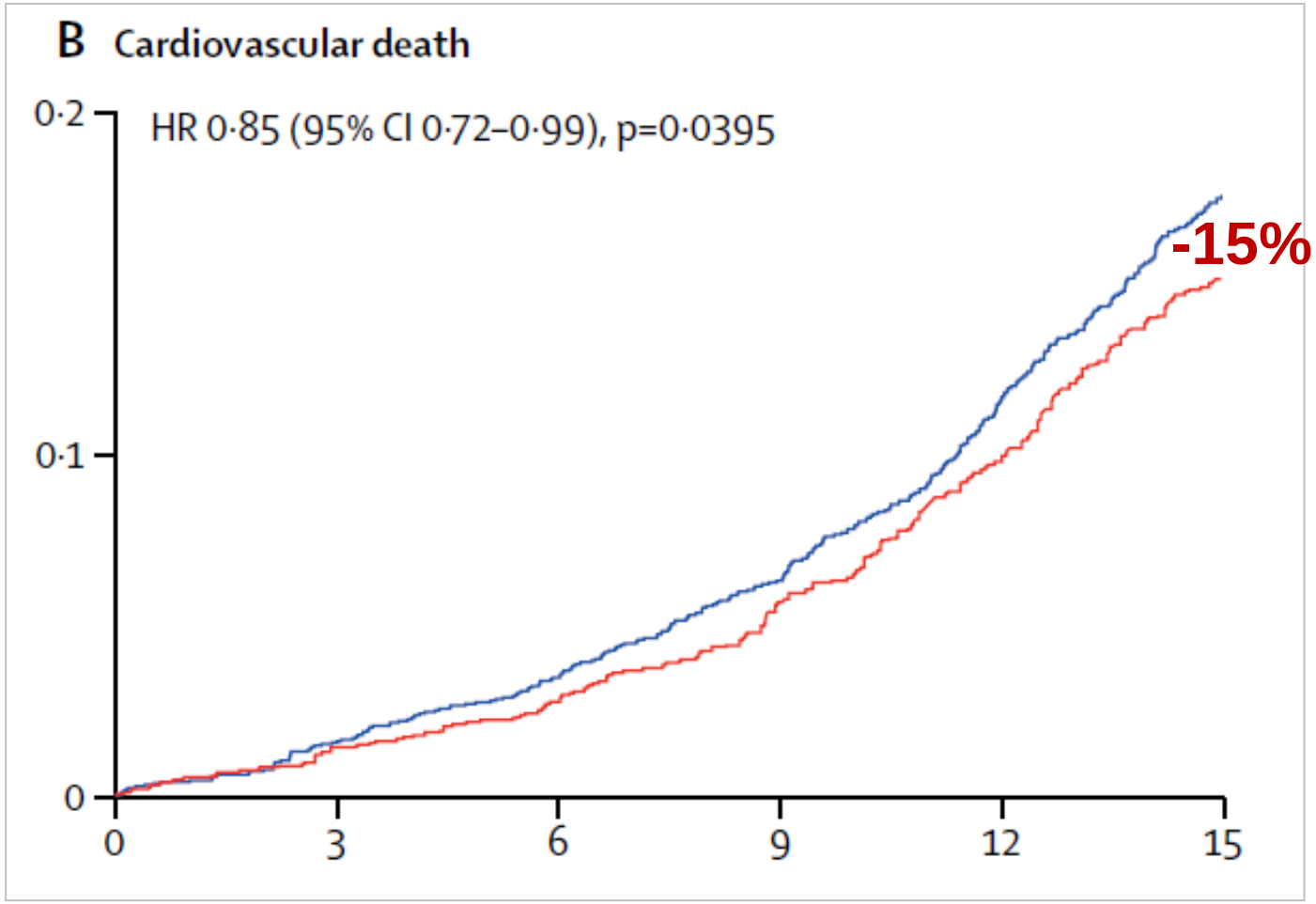
# Long-term mortality after blood pressure-lowering and lipid-lowering treatment in patients with hypertension in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) Legacy study: 16-year follow-up results of a randomised factorial trial

*Ajay Gupta, Judith Mackay, Andrew Whitehouse, Thomas Godec, Tim Collier, Stuart Pocock, Neil Poulter, Peter Sever*

**Interpretation** Our findings show the long-term beneficial effects on mortality of antihypertensive treatment with a calcium channel blocker-based treatment regimen and lipid-lowering with a statin: patients on amlodipine-based treatment had fewer stroke deaths and patients on atorvastatin had fewer cardiovascular deaths more than 10 years after trial closure. Overall, the ASCOT Legacy study supports the notion that interventions for blood pressure and cholesterol are associated with long-term benefits on cardiovascular outcomes.

www.thelancet.com *Published online August 26, 2018*

# Lower risk of CV death with Atorvastatin vs Placebo after 16 years




The mechanisms underlying these observations remain unproven, but it is possible that statin-induced plaque stabilisation occurs during the initial trial, which confers the long-term benefit.

*www.thelancet.com Published online August 26, 2018*

# Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase

*Lancet* 2017; 389: 2473–81

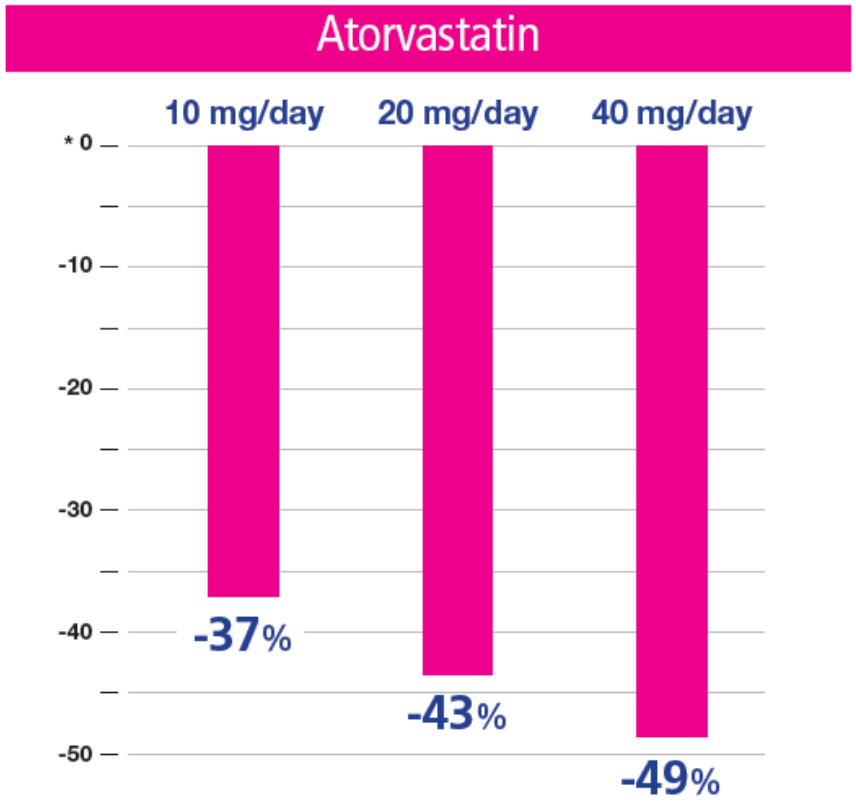
*Ajay Gupta, David Thompson, Andrew Whitehouse, Tim Collier, Bjorn Dahlof, Neil Poulter, Rory Collins, Peter Sever, on behalf of the ASCOT Investigators*

| | Blinded randomised phase (ASCOT-LLA) | | Non-blinded non-randomised phase | |
|---|---|---|---|---|
| | Placebo (n=5079) | Atorvastatin (n=5101) | Atorvastatin non-user (n=3490) | Atorvastatin user (n=6409) |
| **Muscle related** | | | | |
| Patients (n) | 283 | 298 | 124 | 161 |
| AE rate (% per annum) | 2·00% | 2·03% | 1·00% | 1·26% |
| HR (95% CI) | 1 | 1·03 (0·88–1·21) | 1 | 1·41 (1·10–1·79) |
| p value | .. | 0·72 | .. | 0·006 |

**La comparsa di mialgie durante terapia con statina è stata riportata in misura maggiore solo quando i pazienti ed i medici erano a conoscenza del trattamento con statina, e non durante il periodo di trattamento in doppio cieco.**

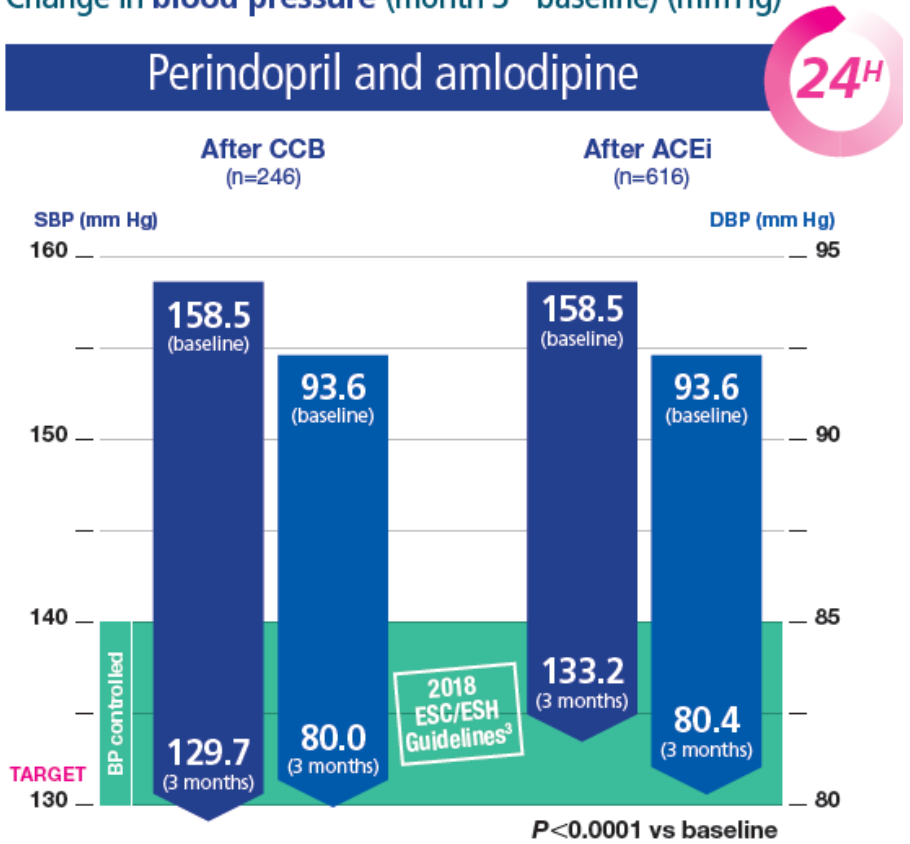
# Polypills – with efficient moleculs

Reduction in serum LDL-C concentration (%)[1]




Meta-analysis of 164 short-term randomized placebo-controlled trials of six statins including atorvastatin. *Absolute reductions (mmol/L) (with 95% confidence intervals) and percentage reductions in serum LDL cholesterol concentration according to statin and daily dose (summary estimates from 164 randomized placebo-controlled trials).

Change in blood pressure (month 3 - baseline) (mm Hg)[2]




Prospective, open-label, longitudinal, phase IV study conducted in 2132 previously-treated uncontrolled and/or intolerant patients. Blood pressure for the overall population dropped from 158.5±17.5/93.66±9.8 mm Hg to 132.9±10.6/80.7±6.2 mm Hg.

ACEi: angiotensin-converting enzyme inhibitor, BP: blood pressure, CCB: calcium channel blocker, LDL-C: low-density lipoprotein cholesterol.

**1.** Law MR, et al. *BMJ.* 2003;326(7404):1423-1427. **2.** Hatala R, et al. *Clin Drug Investig.* 2012;32(9):603-612. **3.** Mancia G, Williams B. Plenary Session: 2018 European Guidelines. European Society of Hypertension 28th European Meeting on Hypertension and Cardiovascular Protection. June 2018; Barcelona, Spain. *The efficacy has been demonstrated with mono-components taken separately: LDL-C with atorvastatin and BP with perindopril and amlodipine.

# Conclusioni

- ✓La coesistenza d'ipertensione ed ipercolesterolemia aumenta in modo additivo l'incidenza di eventi CV ed il trattamento di entrambi i FdR contribuisce significativamente nel ridurre il profilo di rischio CV individuale
- ✓Il trattamento polifarmacologico dev'essere accompagnato da periodiche revisioni al fine di ottimizzarne l'aderenza
- ✓Una strategia costituita dalla combinazione di farmaci di sicura efficacia in SPC (o Polipillola), migliorando l'aderenza ed il controllo dei singoli fattori di rischio, potrebbe contribuire nel ridurre ulteriormente l'incidenza di eventi CV rispetto alla somministrazione delle singole molecole