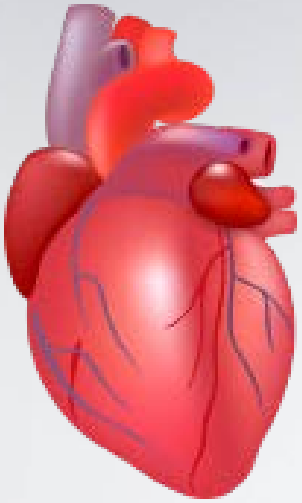


Niciodata nu este prea tarziu sa reduci riscul cardiovascular!

Bogdan Caloian,
Cluj-Napoca

Ghidurile ESC/ESH 2021

new

Regiuni cu risc privind rata **mortalității** cardiovasculare a Organizației Mondiale a Sănătății

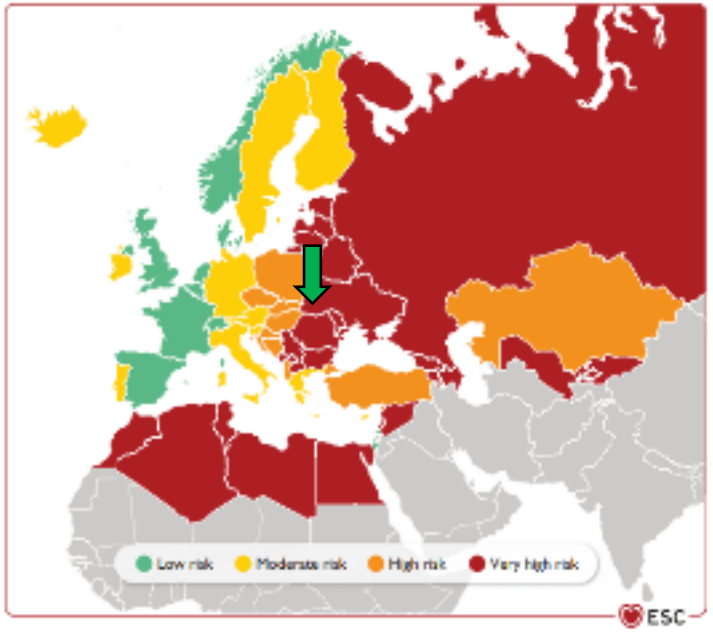
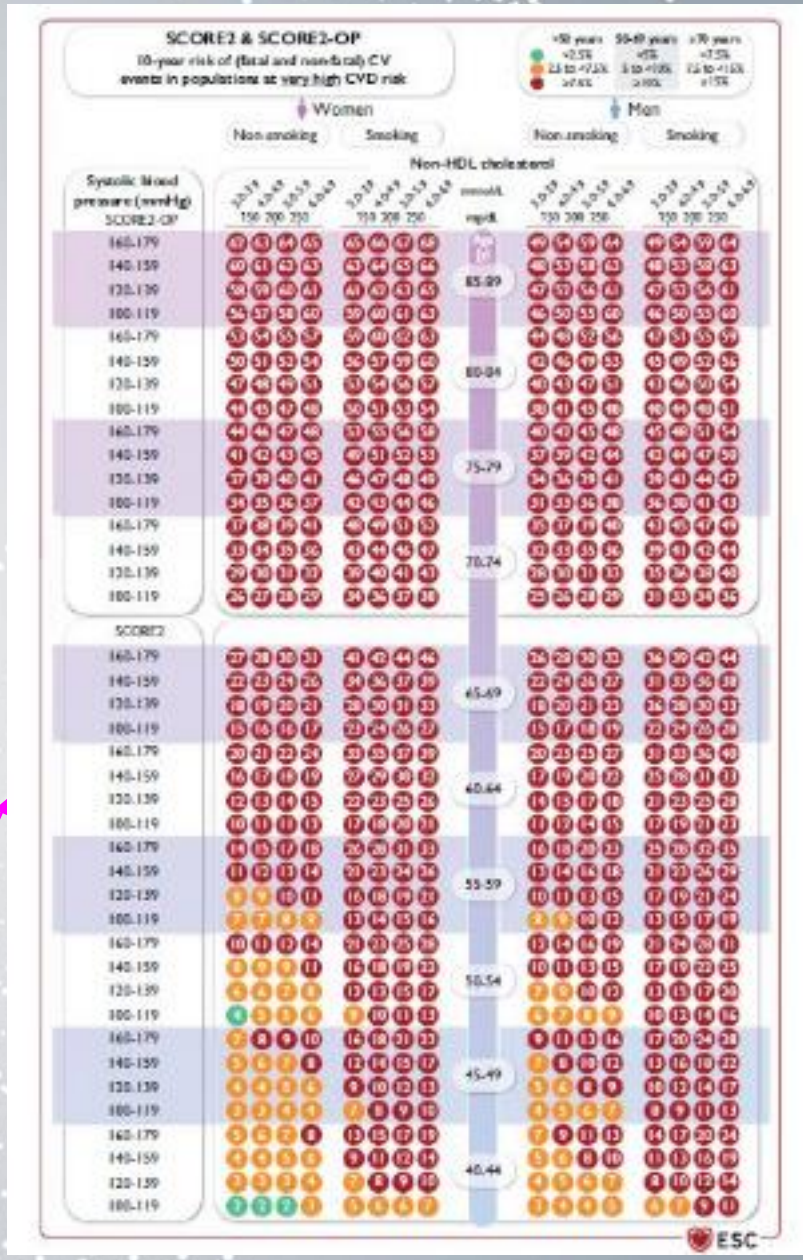


Figure 4 Risk regions based on World Health Organization cardiovascular mortality rates

SCORE2 & SCORE2-OP Harta de risc fatal sau non-fatal (infarct miocardic, **boală aterostclerotică**)

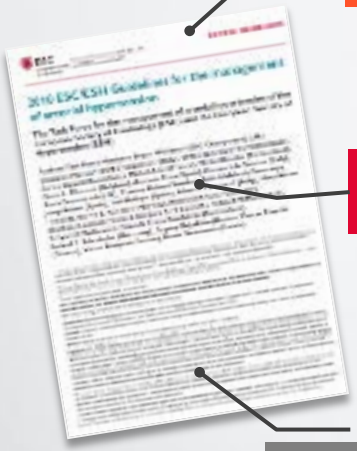


Frank L.J. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. European Heart Journal 2021; 00: 1-111. doi:10.1093/eurheartj/ehab484;

KRKA

Ghidurile de hipertensiune ESH/ESC 2018
Ghidurile de Dislipidemie ESC/EAS 2019,
Noile linii directoare privind HTA și hipercolesterolemia cu noi valori țintă

Ghidurile ESH / ESC 2018 vizează valori ale TA astfel:



< 140/90 mm Hg

Pentru toți pacienții hipertensivi

< 130/80 mm Hg

pentru majoritatea pacienților hipertensivi, **dacă tratamentul este bine tolerat (dar nu mai mic de 120 mm Hg)**

Pentru pacienții vârstnici (≥ 65 ani) **valoarea țintă TAS este 130–139** mm Hg.

Ghidurile ESC / EAS 2019 vizează valorile LDL-c astfel:

	Valoarea LDL-C **țintă**
Pacienți ASCVD care au experimentat al doilea eveniment vascular în ultimii 2 ani*	< 1,0 mmol/L (< 40 mg/dL) ar trebui luat în considerare
Risc foarte înalt în **prevenție primară și secundară**	Se recomandă reducerea cu ≥ 50 % față de valoarea inițială și < 1,4 mmol/L (< 55 mg/dL)
Risc înalt	Se recomandă reducerea cu ≥ 50 % de la valoarea inițială și < 1,8 mmol/L (< 70 mg/dL)
Risc moderat	< 2,6 mmol/L (< 100 mg/dL) ar trebui luat în considerare
Risc **scăzut**	< 3,0 mmol/L (< 116 mg/dL) ar trebui luat în considerare

HTA – hipertensiune arterială, TA – tensiune arterială, TAS – tensiune arterială sistolică,

Williams B, Mancia G, Spiering W et.al. ESC Scientific Document Group; 2018 ESC/ESH Guidelines for the management of arterial hypertension, European Heart Journal 2018; 39 (33): 3021–104.
Reference: Mach F, Baigent C, Catapano AL et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Euro Heart Jour. 2019; 00: 1-78. doi:10.1093/eurheartj/ehz455.

KRKA

EUROASPIRE V

PREVENȚIE PRIMARĂ

European Journal of Preventive Cardiology
ESC European Society of Cardiology

Full research paper

Primary prevention efforts are poorly developed in people at high cardiovascular risk: A report from the European Society of Cardiology EURObservational Research Programme EUROASPIRE V survey in 16 European countries

European Journal of Preventive Cardiology
0(00) 1–13

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Principal findings

The EUROASPIRE V survey in primary care clearly demonstrates that a large majority of patients at high CVD risk fail to achieve lifestyle, blood pressure, lipid and glycaemic targets as defined in the 2016 JES guidelines on CVD prevention in clinical practice. A wide gap still exists between the evidence-based guidelines and everyday clinical practice.

PREVENȚIE SECUNDARĂ

European Journal of Preventive Cardiology
ESC European Society of Cardiology

Full research paper

Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: Results from the European Society of Cardiology ESC-EORP EUROASPIRE V registry

European Journal of Preventive Cardiology
2019, Vol. 26(8) 824–835

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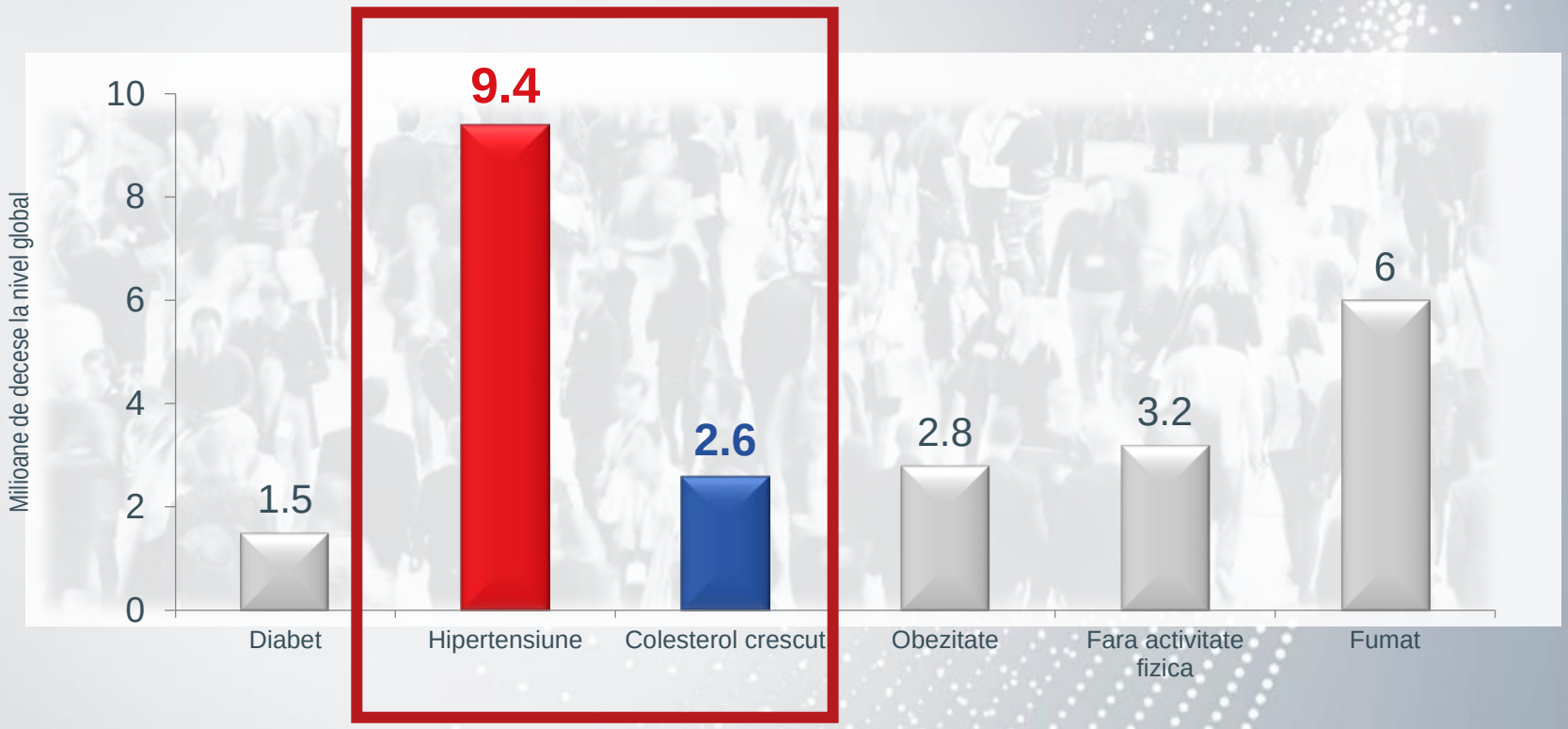
prevalence of diabetes and its control. Despite the high use of cardioprotective drug therapies the majority of patients did not achieve their blood pressure, LDL-C and glucose targets.

* or a reduction of at least 50% if the baseline LDL-C is between 2.6 and 5.2 mmol/L

Kotseva K, De Backer G, De Bacquer D et.al. Primary prevention efforts are poorly developed in people at high cardiovascular risk: A report from the European Society of Cardiology EURObservational Research Programme EUROASPIRE V survey in 16 European countries. Eur J Prev Cardiol. 2020; Mar 20: 2047487320908698.

KRKA

Gestionarea hipertensiunii si a hiperlipidemiei – elementele de bază pentru prevenirea bolii cardiovasculare



1. World Heart Federation. Cardiovascular disease risk factors [Internet]. [cited 2019 Sept 23]. Available from: http://www.world-heart-federation.org/ fileadmin/user_upload/documents/Fact_sheets/2012/PressBackgrounderApril2012RiskFactors.pdf. 2. WHO | Diabetes [Internet]. WHO. [cited 2019 Sept 23]. Available from: http://www.who.int/mediacentre/factsheets/fs312/en/. 3. Health CO on S and. Smoking and Tobacco Use; Fact Sheet; Fast Facts [Internet]. Smoking and Tobacco Use. [cited 2019 Sept 23]. Available from: http://www.cdc.gov/tobacco/data_statistics/fact_sheets/fast_facts/. 4. Dominiczak AF, Kuo DRK. Hypertension: Update 2015. Hypertension. 2015 Jan 1;65(1):3–4.

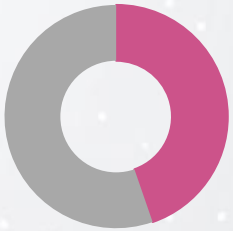
Managementul hipertensiunii și al hipercolesterolemiei – cheia prevenției evenimentelor CV

- LDL-c scăzut

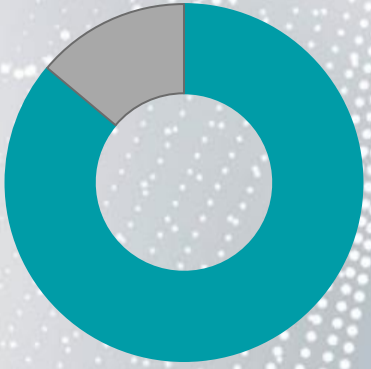
54,2% reducerea riscului
de evenimente CV majore

- TAS scăzută

44,7% reducerea riscului
de evenimente CV majore



LDL-c și TAS scăzute



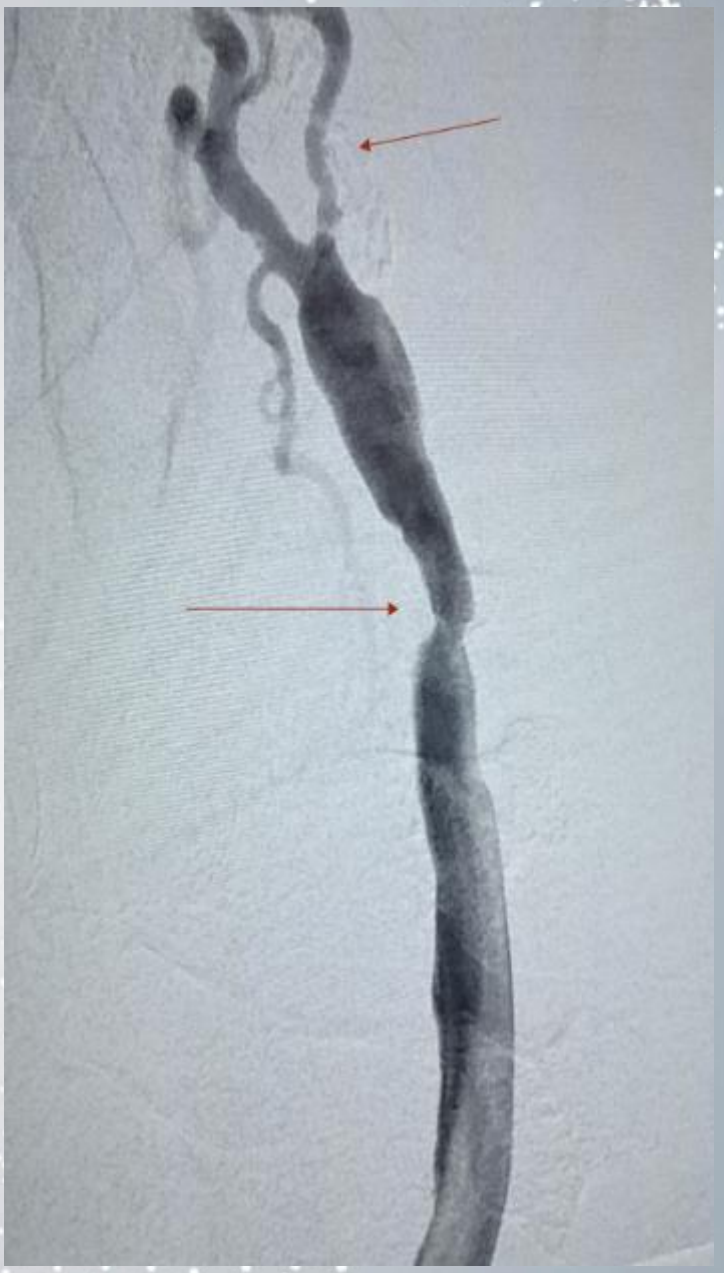
86,1% reducerea riscului
de evenimente CV majore

LDL-c – LDL colesterol, TAS – tensiune arterială sistolică, BCV - boală cardiovasculară, CV - cardiovascular

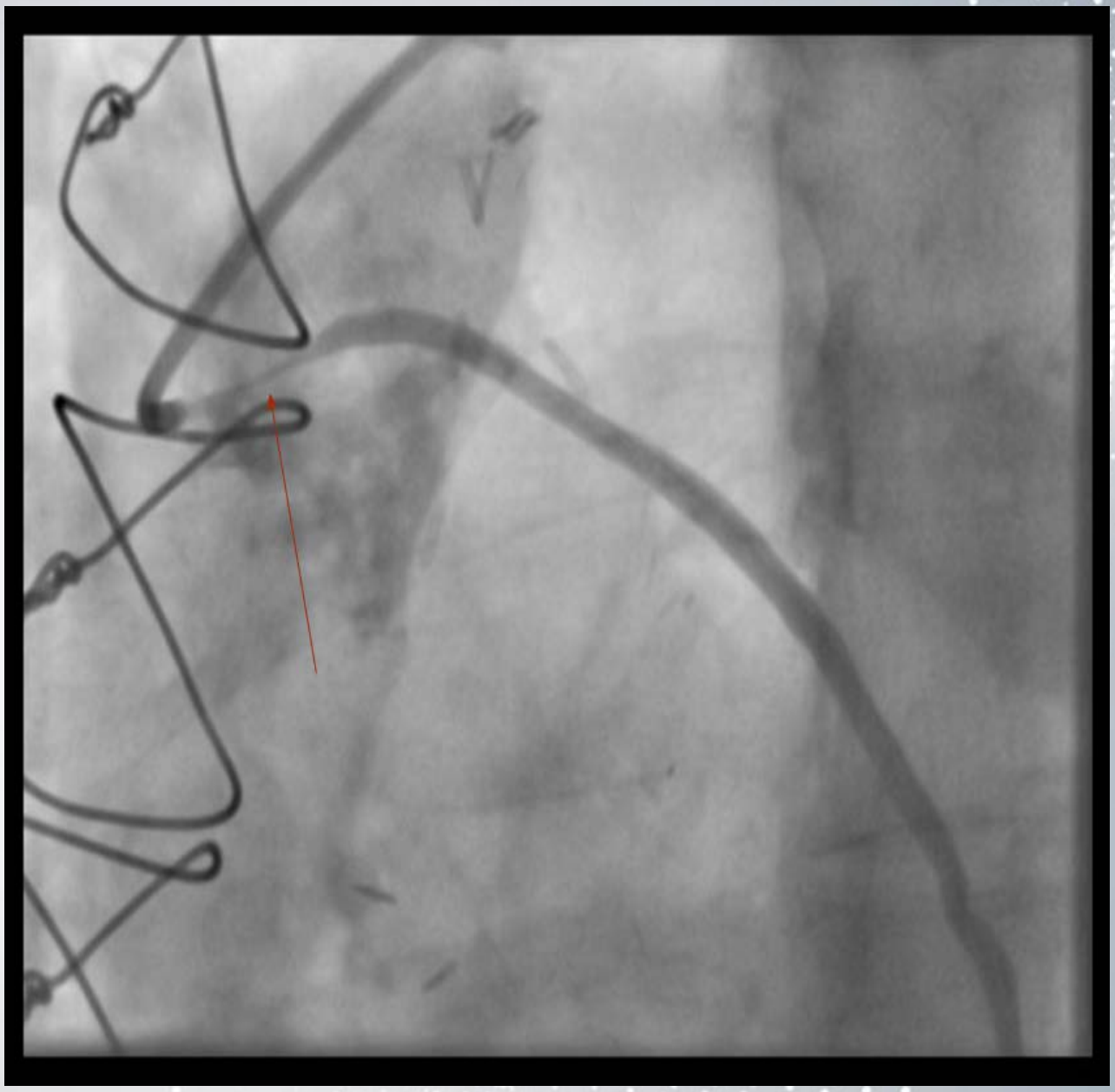
Long-Term Exposure to Moderately Lower LDL-C and SBP May Lower Lifetime Risk of CVD. ACC Aug 2016 [cited 14. 2. 2017]
http://www.acc.org/latest-in-cardiology/articles/2016/08/26/17/20/8am-mon-effect-of-long-term-exposure-to-lower-ldl-c-lower-sbp-or-both-on-the-risk-of-cvd-esc-2016?w_nav=LC

Caz

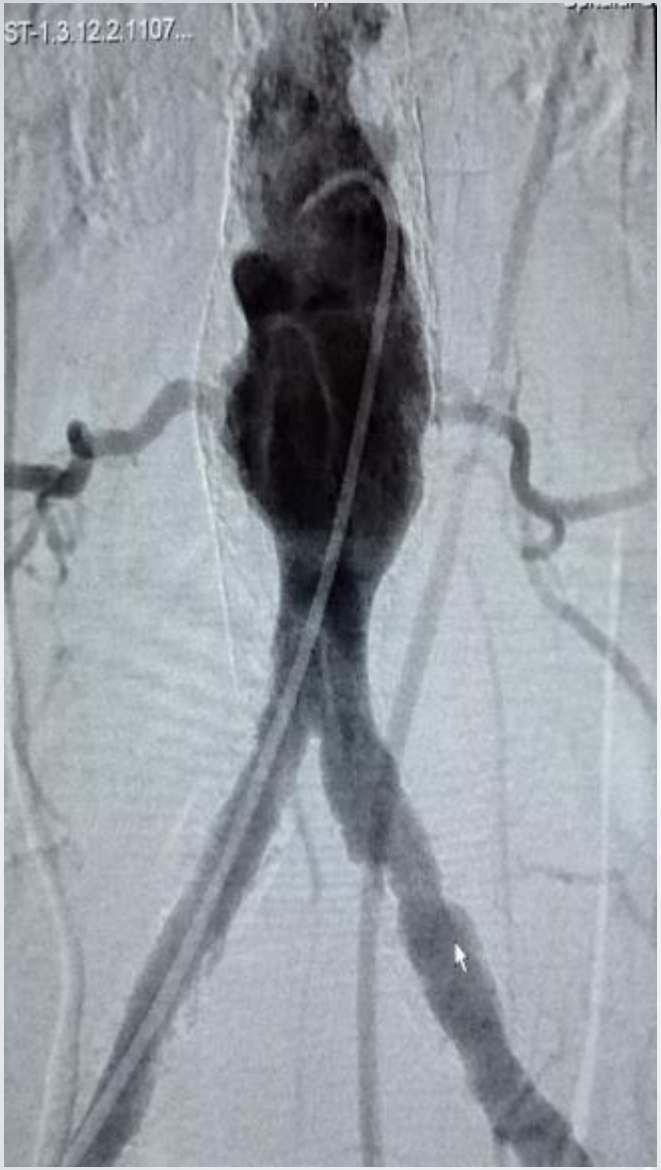
- Pacient de 76 de ani
- Hipertensiv, obez, fost fumator
- Dislipidemic (LDL-C=160mg/dL)
- Diabet zaharat tip II (14 ani), in tratament cu Insulina si Metformin
- Nefropatie diabetica si hipertensiva (eGFR=51mL/min/1.73m2)
- Leziuni aterosclerotice in multiple teritorii vasculare:
  - Carotide
  - Coronare (Bypass aortocoronarian, stenoza severa graft venos, revascularizare percutana)
  - Aorta
  - Sistem arterial membre inferioare (revascularizare percutana)



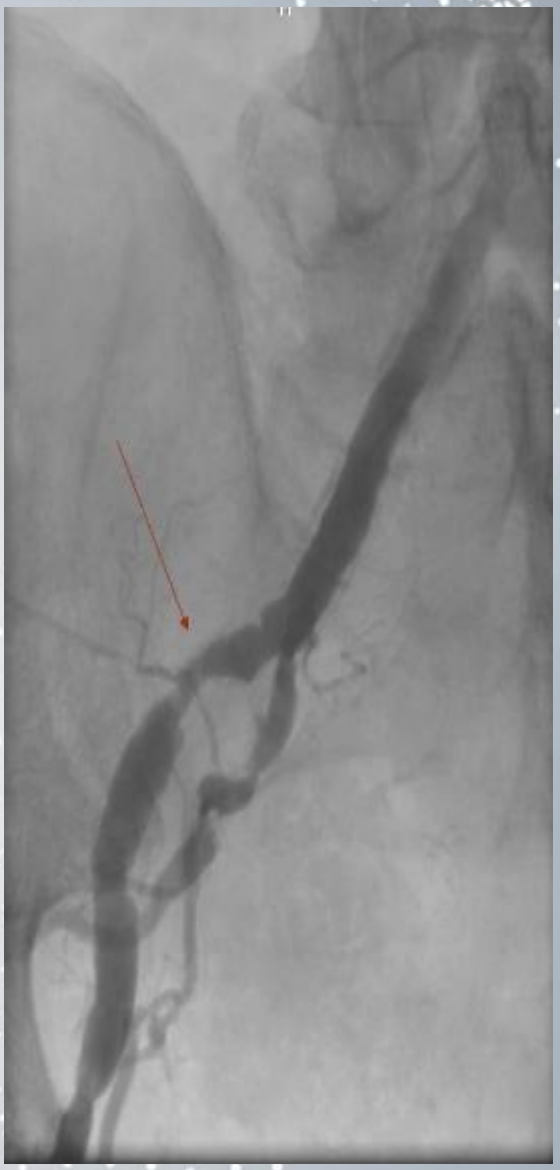
Arteriografie carotidiana



Bypass Ao-coronarian, stenoza graft venos



Anevrism de aorta abdominala



Stenoza a. iliaca ext dreapta

Table 5 Ten year cardiovascular risk categories (Systematic COronary Risk Evaluation system)

Very high risk	People with any of the following:
	Documented CVD, either clinical or unequivocal on imaging. • **Clinical CVD** includes acute myocardial infarction, acute coronary syndrome, coronary or other arterial revascularization, stroke, TIA, aortic aneurysm, and PAD • **Unequivocal documented CVD on imaging** includes significant plaque (i.e. ≥50% stenosis) on angiography or ultrasound; it does not include increase in carotid intima-media thickness • **Diabetes mellitus with target organ damage**, e.g. proteinuria or a with a major risk factor such as grade 3 hypertension or hypercholesterolaemia • **Severe CKD** (eGFR <30 mL/min/1.73 m^2) • **A calculated 10 year SCORE of ≥10%**
High risk	People with any of the following: • **Marked elevation of a single risk factor**, particularly cholesterol >8 mmol/L (>310 mg/dL), e.g. familial hypercholesterolaemia or grade 3 hypertension (BP ≥180/110 mmHg) • **Most other people with diabetes mellitus** (except some young people with type 1 diabetes mellitus and without major risk factors, who may be at moderate-risk)
	Hypertensive LVH
	Moderate CKD eGFR 30-59 mL/min/1.73 m^2)
	A calculated 10 year SCORE of 5-10%
Moderate risk	People with: • **A calculated 10 year SCORE of ≥1 to <5%** • **Grade 2 hypertension** • **Many middle-aged people belong to this category**
Low risk	People with: • **A calculated 10 year SCORE of <1%**

BP = blood pressure; CKD = chronic kidney disease; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; LVH = left ventricular hypertrophy; TIA = transient ischaemic attack; PAD = peripheral artery disease; SCORE = Systematic COronary Risk Evaluation.

- Medicatia actuala:
  - Bisoprolol 5mg/zi
  - Clopidogrel 75mg/zi
  - Enalapril 10mg 1-0-0
  - Indapamid 1.5mg 1-0-0
  - Simvastatina 20mg/zi
  - Isosorbid mononitrate 2x40mg/zi

Putem imbunatati planul terapeutic al acestui pacient?

Toti IECA sunt la fel?

Not All Angiotensin-Converting Enzyme Inhibitors Are Equal: Focus on Ramipril and Perindopril

DOI: 10.3810/pgm.2013.07.2687

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Carl J. Lavie, MD[2,3]
James H. O'Keefe, MD[4]

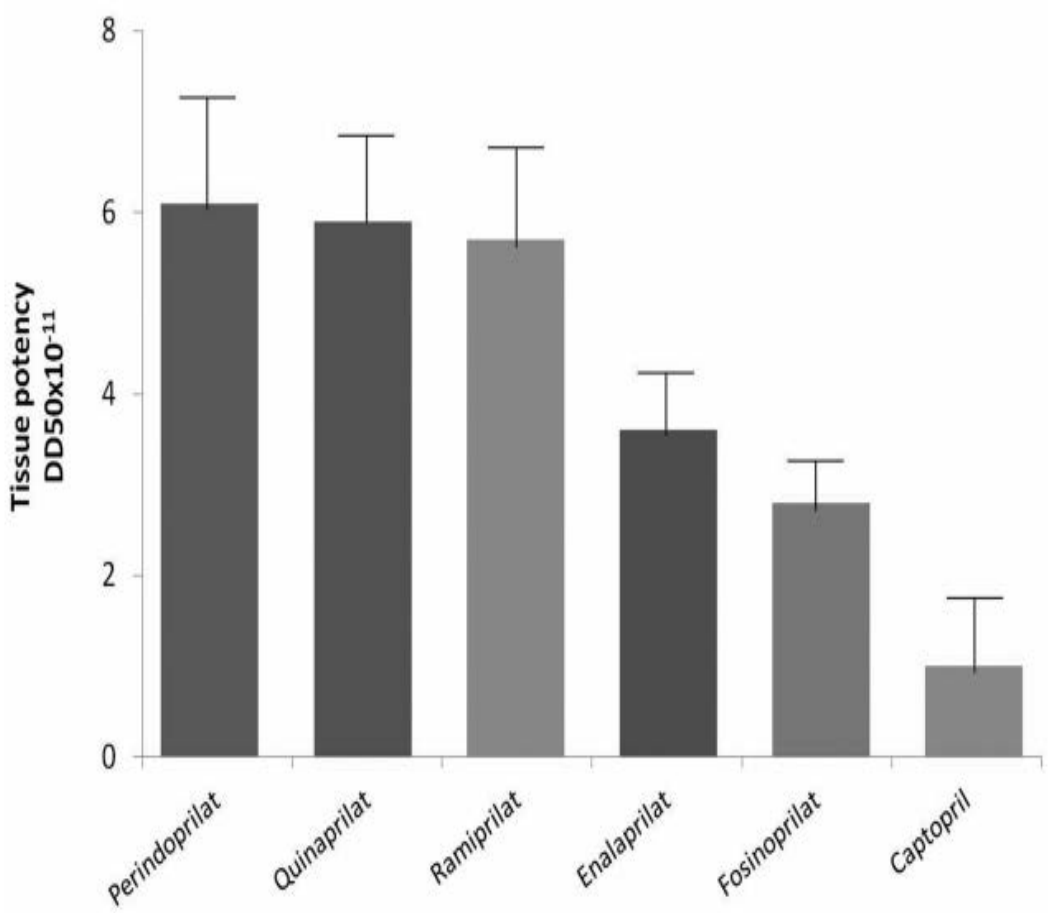
[1]Wegmans Pharmacy, Ithaca, NY; [2]John Ochsner Heart and Vascular Institute, Ochsner Clinical School/University of Queensland School of Medicine, New Orleans, LA; [3]Pennington Biomedical Research Center, Baton Rouge, LA; [4]Mid America Heart Institute at Saint Luke's Hospital, University of Missouri–Kansas City, Kansas City, MO

Abstract: Angiotensin-converting enzyme (ACE) inhibitors are a heterogeneous class, varying in pharmacologic properties, which have different therapeutic impacts on patient profiles, including lipophilicity, tissue–ACE binding, duration of action, half-life, and increased bradykinin availability. Among the ACE inhibitor class, the agent perindopril, in particular, has pleiotropic effects that are not equally shared by other ACE inhibitors, including bradykinin site selectivity and subsequent enhancement of nitric oxide and inhibition of endothelial cell apoptosis. Moreover, there is a large amount of evidence to suggest that perindopril therapy may reduce cardiovascular event rates in patients, yet perindopril is rarely prescribed in the United States. Ramipril is another ACE inhibitor with both a favorable clinical profile and impressive outcomes data. Our review compares the pharmacologic and trial data among perindopril, ramipril, and other ACE inhibitors. In patients with or at high risk for coronary heart disease who do not have heart failure, or in patients with heart failure with preserved ejection fraction, perindopril should be among the preferred treatment agents in the ACE inhibitor class. Ramipril has an impressive track record of improving cardiovascular outcomes, too, and should be considered a preferred agent among the ACE inhibitor class.

Keywords: angiotensin-converting enzyme inhibitor; bradykinin; heart failure; cardiovascular disease; ramipril; perindopril

Afinitatea tisulara

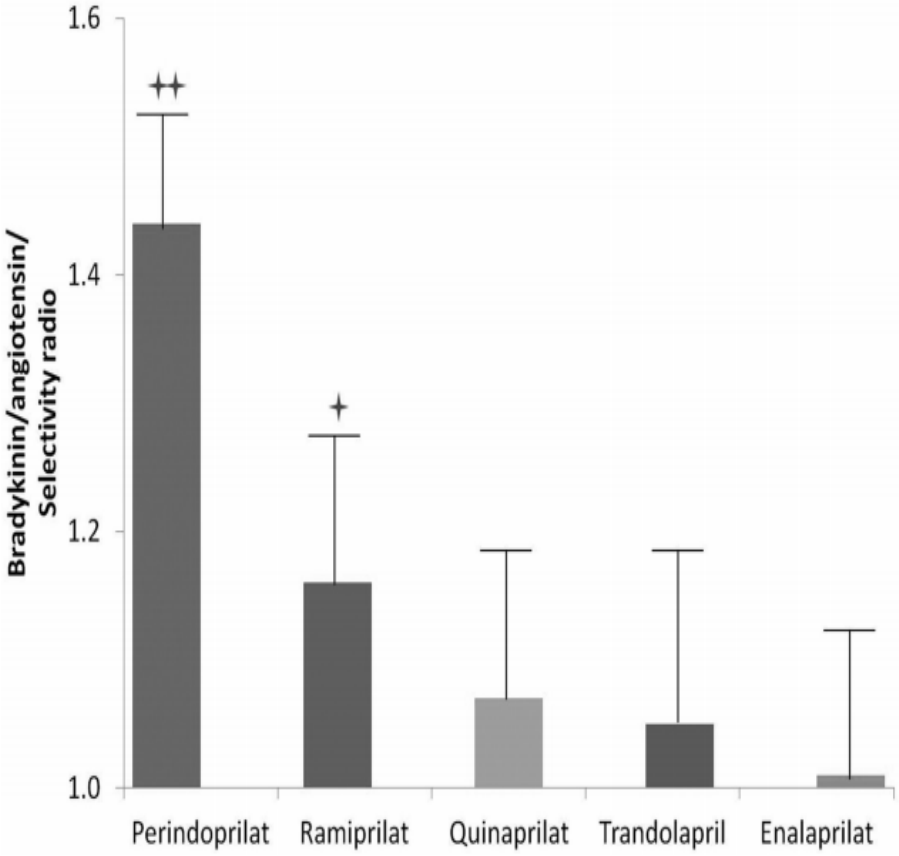
Figure 1. Tissue affinity of various ACEIs: DD50, ACEI concentration required for 50% displacement of bound radioligand.[5]



DiNicolantonio et al

Selectivitatea pentru receptorii de AT I si BK

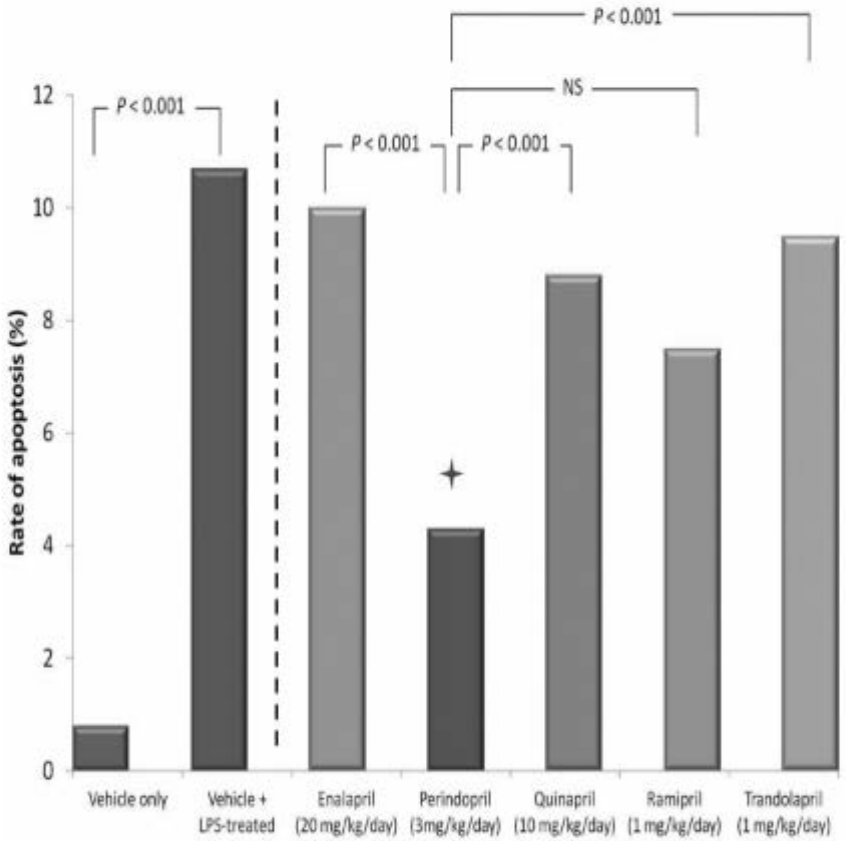
Figure 2. Relative selectivity of tested ACEIs for bradykinin vs angiotensin I binding sites. $P < 0.001$ by ANOVA for repeated measures; $^{**}P < 0.001$ vs ramiprilat, quinaprilat, trandolaprilat, and enalaprilat; $^{*}P < 0.01$ vs enalaprilat[8]



DiNicolantonio et al

Rata apoptozei celulelor endoteliale

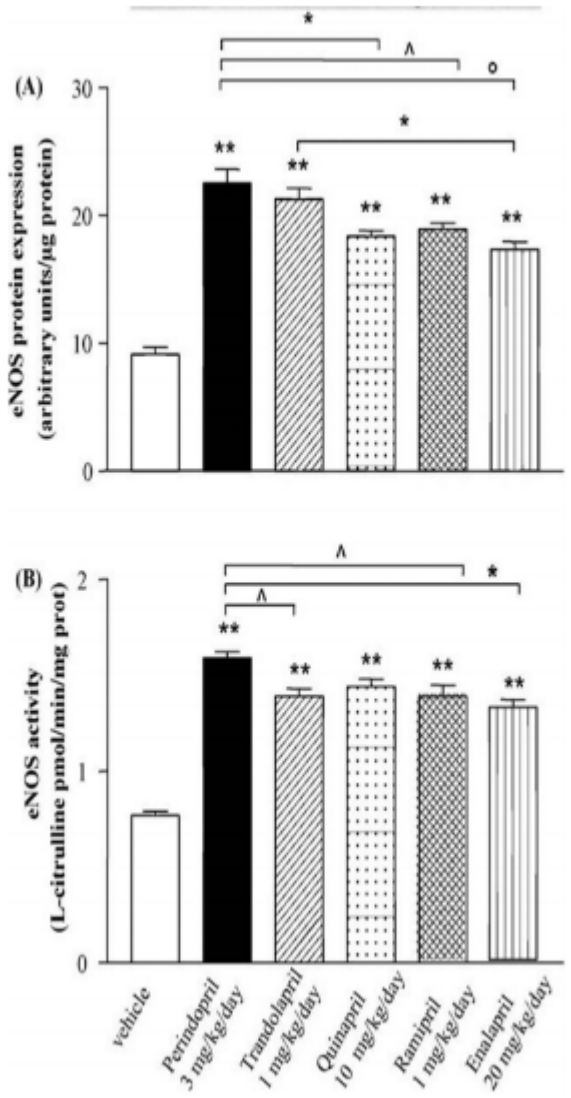
Figure 3. Rate of apoptosis in rats treated for 7 days with ACEI or vehicle only (control) expressed as the percentage of annexin V-positive rat aortic endothelial cells following lipopolysaccharide-induced apoptosis. *$P < 0.001$ vs control.[11,57]



DiNicolantonio et al

Productia de oxid nitric (NO)

Figure 4. Endothelial nitric oxide synthase (eNOS) protein expression (**A**) and activity (**B**) in the descending aorta of rats treated with different ACEIs. (**) $P < 0.001$ vs vehicle, (°) $P < 0.001$, (*)$P < 0.01$ and (^)$P < 0.05$ each ACEI vs others. In each group of treatment, 5 animals were employed.[14]



DiNicolantonio et al

Indapamida sau alt diuretic?

Head-to-Head Comparisons of Hydrochlorothiazide With Indapamide and Chlorthalidone

Antihypertensive and Metabolic Effects

George C. Roush, Michael E. Ernst, John B. Kostis, Suraj Tandon, Domenic A. Sica

See Editorial Commentary, pp 983–984

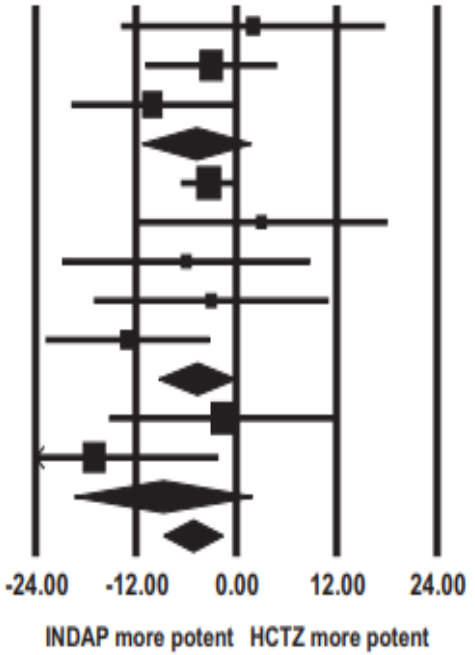
Abstract—Hydrochlorothiazide (HCTZ) has often been contrasted with chlorthalidone, but relatively little is known about HCTZ versus indapamide (INDAP). This systematic review retrieved 9765 publications, and from these, it identified 14 randomized trials with 883 patients comparing HCTZ with INDAP and chlorthalidone on antihypertensive potency or metabolic effects. To make fair comparisons, the dose of the diuretic in each arm was assigned 1 of 3 dose levels. In random effects meta-analysis, INDAP and chlorthalidone lowered systolic blood pressure more than HCTZ: −5.1 mm Hg (95% confidence interval, −8.7 to −1.6); P=0.004 and −3.6 mm Hg (95% confidence interval, −7.3 to 0.0); P=0.052, respectively. For both comparisons, there was minimal heterogeneity in effect across trials and no evidence for publication bias. The HCTZ–INDAP contrast was biased in favor of greater HCTZ potency because of a much greater contribution to the overall effect from trials in which the HCTZ arm had a higher dose level than the INDAP arm. For the HCTZ–INDAP comparison, no single trial was responsible for the overall result nor was it possible to detect significant modifications of this comparison by duration of follow-up, high- versus low-bias trials, or the presence or absence of background medications. There were no detectable differences between HCTZ and INDAP in metabolic adverse effects, including effects on serum potassium. In conclusion, these head-to-head comparisons demonstrate that, like chlorthalidone, INDAP is more potent than HCTZ at commonly prescribed doses without evidence for greater adverse metabolic effects. (***Hypertension*. 2015;65:1041-1046. DOI: 10.1161/HYPERTENSIONAHA.114.05021.)** • Online Data Supplement

Key Words: blood pressure ■ chlorthalidone ■ hydrochlorothiazide ■ hypokalemia ■ indapamide

Group by Dose Level	Study name	Difference in means	Lower limit	Upper limit	p-Value
Dose Equivalent	Elliott	2.000	-13.680	17.680	0.803
Dose Equivalent	Malini	-3.000	-10.785	4.785	0.450
Dose Equivalent	Spence	-10.050	-19.642	-0.458	0.040
Dose Equivalent		-4.744	-11.254	1.767	0.153
HCTZ Higher	Emeriau	-3.300	-6.542	-0.058	0.046
HCTZ Higher	Kreeft	3.000	-11.987	17.987	0.695
HCTZ Higher	Madkour	-6.000	-20.743	8.743	0.425
HCTZ Higher	Plante a	-3.000	-16.960	10.960	0.674
HCTZ Higher	Plante b	-13.000	-22.705	-3.295	0.009
HCTZ Higher		-4.657	-9.225	-0.089	0.046
INDAP Higher	Krum	-1.600	-15.146	11.946	0.817
INDAP Higher	Radevski	-17.000	-31.761	-2.239	0.024
INDAP Higher		-8.717	-19.345	1.910	0.108
Overall		-5.130	-8.657	-1.602	0.004

Statistics for each study

Difference in means and 95% CI



Regression of left ventricular hypertrophy in hypertensive patients treated with indapamide SR 1.5 mg versus enalapril 20 mg: the LIVE study

Philippe Gosse[a], Desmond J. Sheridan[b], Faiez Zannad[c], Olivier Dubourg[d], Pascal Guéret[e], Yuri Karpov[f], Peter W. de Leeuw[g], Jose-Luis Palma-Gamiz[h], Achille Pessina[i], Wolfgang Motz[j], Jean-Paul Degaute[k] and Claude Chastang[l], on behalf of the LIVE investigators

Objective To compare the efficacy of indapamide sustained release (SR) 1.5 mg and enalapril 20 mg at reducing left ventricular mass index (LVMI) in hypertensive patients with left ventricular hypertrophy (LVH).

Design The LIVE study (left ventricular hypertrophy regression, indapamide versus enalapril) was a 1 year, prospective, randomized, double-blind study. For the first time, a committee validated LVH before inclusion, provided on-going quality control during the study, and performed an end-study reading of all echocardiograms blinded to sequence.

Setting European hospitals, general practitioners and cardiologists.

Patients Hypertensive patients aged ⩾ 20 years with LVH (LVMI in men > 120 g/m^2; LVMI in women > 100 g/m^2). Data were obtained from 411 of 505 randomized patients.

Interventions Indapamide SR 1.5 mg, or enalapril 20 mg, daily for 48 weeks.

Main outcome measures LVMI variation in the per-protocol population.

Results Indapamide SR 1.5 mg significantly reduced LVMI (−8.4 ± 30.5 g/m^2 from baseline; $P < 0.001$), but enalapril 20 mg did not (−1.9 ± 28.3 g/m^2). Indapamide SR 1.5 mg reduced LVMI significantly more than enalapril 20 mg: −6.5 g/m^2, $P = 0.013$ (−4.3 g/m^2 when adjusted for baseline values; $P = 0.049$). Both drugs equally and significantly reduced blood pressures ($P < 0.001$), without correlation with LVMI changes. Indapamide SR progressively reduced wall thicknesses throughout the 1-year treatment period. In contrast, the effect of enalapril observed at 6 months was not maintained at 12 months.

Conclusions Indapamide SR 1.5 mg was significantly more effective than enalapril 20 mg at reducing LVMI in hypertensive patients with LVH. *J Hypertens* 18:1465–1475

Journal of Hypertension 2000, **18**:1465–1475

Keywords: hypertension, left ventricular hypertrophy, left ventricular mass, echocardiography, diuretic, angiotensin converting enzyme inhibitor, indapamide SR 1.5 mg; enalapril 20 mg

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Sponsorship: This study was supported by the Institut de Recherches Internationales Servier, Courbevoie, France.

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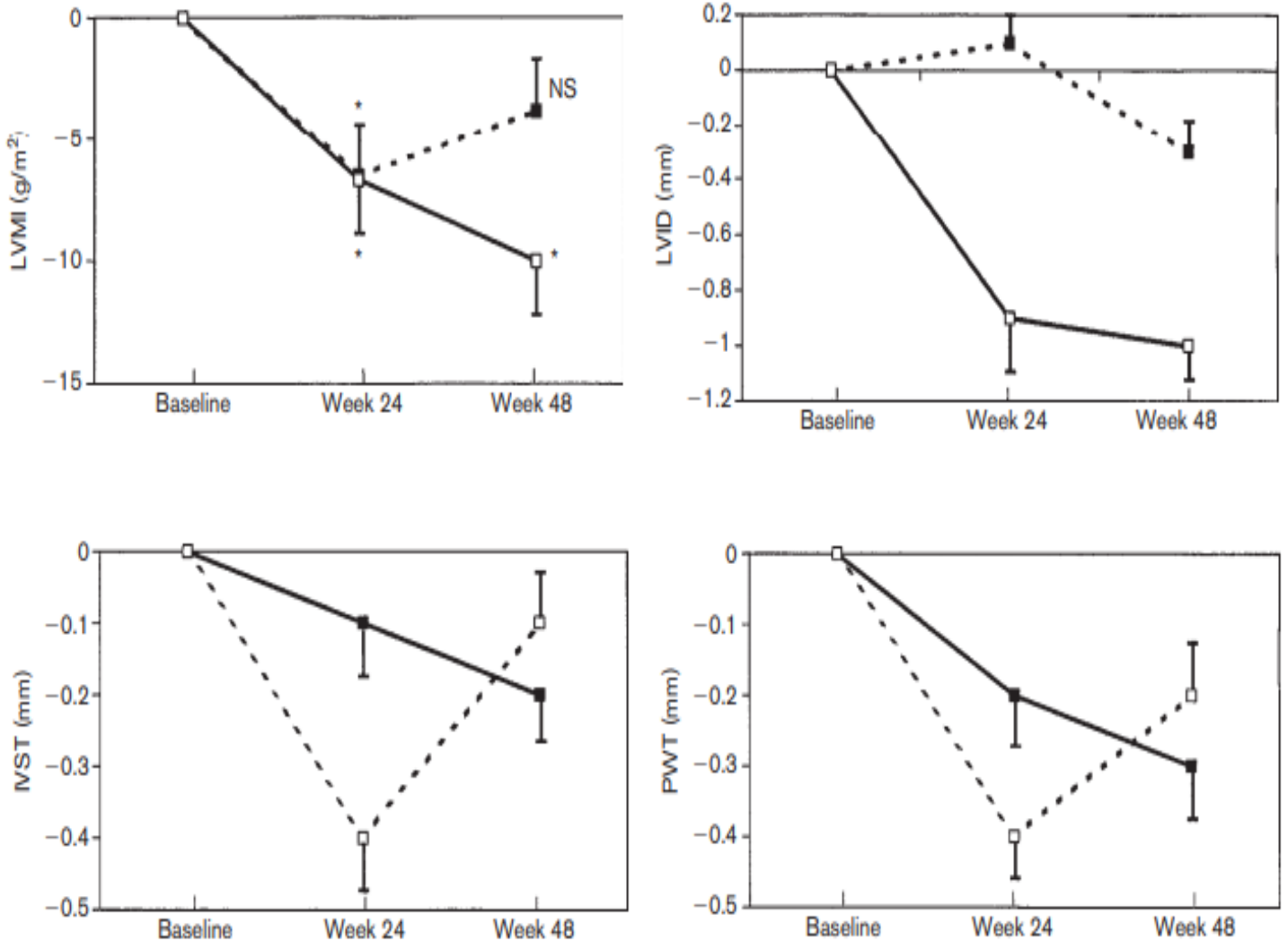
Received 25 November 1999 **Revised** I June 2000
Accepted 27 June 2000



Change in left ventricular mass and its components in the subgroup of patients treated for 1 year ($n = 269$). LVMI, left ventricular mass index; IVST, inter-ventricular septum thickness; PWT, posterior wall thickness; LVID, left ventricular internal diameter; indapamide SR 1.5 mg ($n = 130$, solid line); enalapril 20 mg ($n = 139$, dotted line). Analysis of variance on repeated measures (visit): significant time effect for indapamide SR ($P < 0.001$) and enalapril ($P = 0.046$). Newman–Keuls performed on LVMI: W24 (or W48) versus baseline: $^{*}P < 0.05$; $P > 0.05$: not significant (NS) (W48 versus W24 is not significant whatever the treatment group).

Equivalence of indapamide SR and enalapril on microalbuminuria reduction in hypertensive patients with type 2 diabetes: The NESTOR* study

Marre, Michel[a]; Puig, Juan Garcia[b]; Kokot, Franciszek[c]; Fernandez, Margarita[d]; Jermendy, György[e]; Opie, Lionel[f]; Moyseev, Valentin[g]; Scheen, André[h]; Ionescu-Tirgoviste, Constantin[i]; Saldanha, M Helena[j]; Halabe, Aaron[k]; Williams, Bryan[l]; Mion, Decio Jr[m]; Ruiz, Maximino[n]; Hermansen, Kjeld[o]; Tuomilehto, Jaakko[p]; Finizola, Bartolomé[q]; Gallois, Yves[r]; Amouyel, Philippe[s]; Ollivier, Jean-Pierre[t]; Asmar, Roland[u]

Journal of Hypertension: August 2004 - Volume 22 - Issue 8 - p 1613-1622
doi: 10.1097/01.hjh.0000133733.32125.09
Original papers: Therapeutic asepcts and trials

Abstract | Author Information | Article Metrics

Objectives To test whether microalbuminuria in patients with type 2 diabetes and hypertension is primarily dependent on the severity of hypertension, and to compare the effectiveness of two antihypertensive drugs with opposite effects on the renin–angiotensin system [the diuretic, indapamide sustained release (SR), and an angiotensin-converting enzyme inhibitor, enalapril] in reducing microalbuminuria.

Design A multinational, multicentre, controlled, double-blind, double-dummy, randomized, two-parallel-groups study over 1 year.

Methods After a 4-week placebo run-in period, 570 patients (ages 60.0 ± 9.9 years, 64% men) with type 2 diabetes, essential hypertension [systolic blood pressure (SBP) 140–180 mmHg, and diastolic blood pressure (DBP) < 110 mmHg], and persistent microalbuminuria (20–200 µg/min) were allocated randomly to groups to receive indapamide SR 1.5 mg (***n*** = 284) or enalapril 10 mg (***n*** = 286) once a day. Amlodipine, atenolol, or both were added, if necessary, to achieve the target blood pressure of 140/85 mmHg.

Results There was a significant reduction in the urinary albumin : creatinine ratio. Mean reductions were 35% [95% confidence interval (CI) 24 to 43] and 39% (95% CI 30 to 47%) in the indapamide SR and enalapril groups, respectively. Equivalence was demonstrated between the two groups [1.08 (95% CI 0.89 to 1.31%); ***P*** = 0.01]. The reductions in mean arterial pressure (MAP) were 16.6 ± 9.0 mmHg for the indapamide SR group and 15.0 ± 9.1 mmHg for the enalapril group (NS); the reduction in SBP was significantly greater (***P*** = 0.0245) with indapamide SR. More than 50% of patients in each group required additional antihypertensive therapy, with no differences between groups. Both treatments were well tolerated.

Conclusions Indapamide-SR-based therapy is equivalent to enalapril-based therapy in reducing microalbuminuria with effective blood pressure reduction in patients with hypertension and type 2 diabetes.

7.5.1.3. Thiazide/thiazide-like diuretics (e.g. chlorthalidone and indapamide)

Diuretics have remained the cornerstone of antihypertensive treatment since their introduction in the 1960s. Their effectiveness in preventing all types of CV morbidities and mortality has been confirmed in RCTs and meta-analyses.[300] Diuretics also appear to be more effective than other drug classes in preventing heart failure.[292] There

Drug treatment strategy for hypertension

Recommendations	Class[a]	Level[b]
Among all antihypertensive drugs, ACE inhibitors, ARBs, beta-blockers, CCBs, and diuretics (thiazides and thiazide-like drugs such as chlorthalidone and indapamide) have demonstrated effective reduction of BP and CV events in RCTs, and thus are indicated as the basis of antihypertensive treatment strategies.[2]	I	A
Combination treatment is recommended for most hypertensive patients as initial therapy. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or diuretic. Other combinations of the five major classes can be used.[233,318,327,329,341–345]	I	A

Au dovezi clare cand sunt utilizate individual.
Dar cum functioneaza impreuna?

Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial

Lancet 2007; 370: 829–40

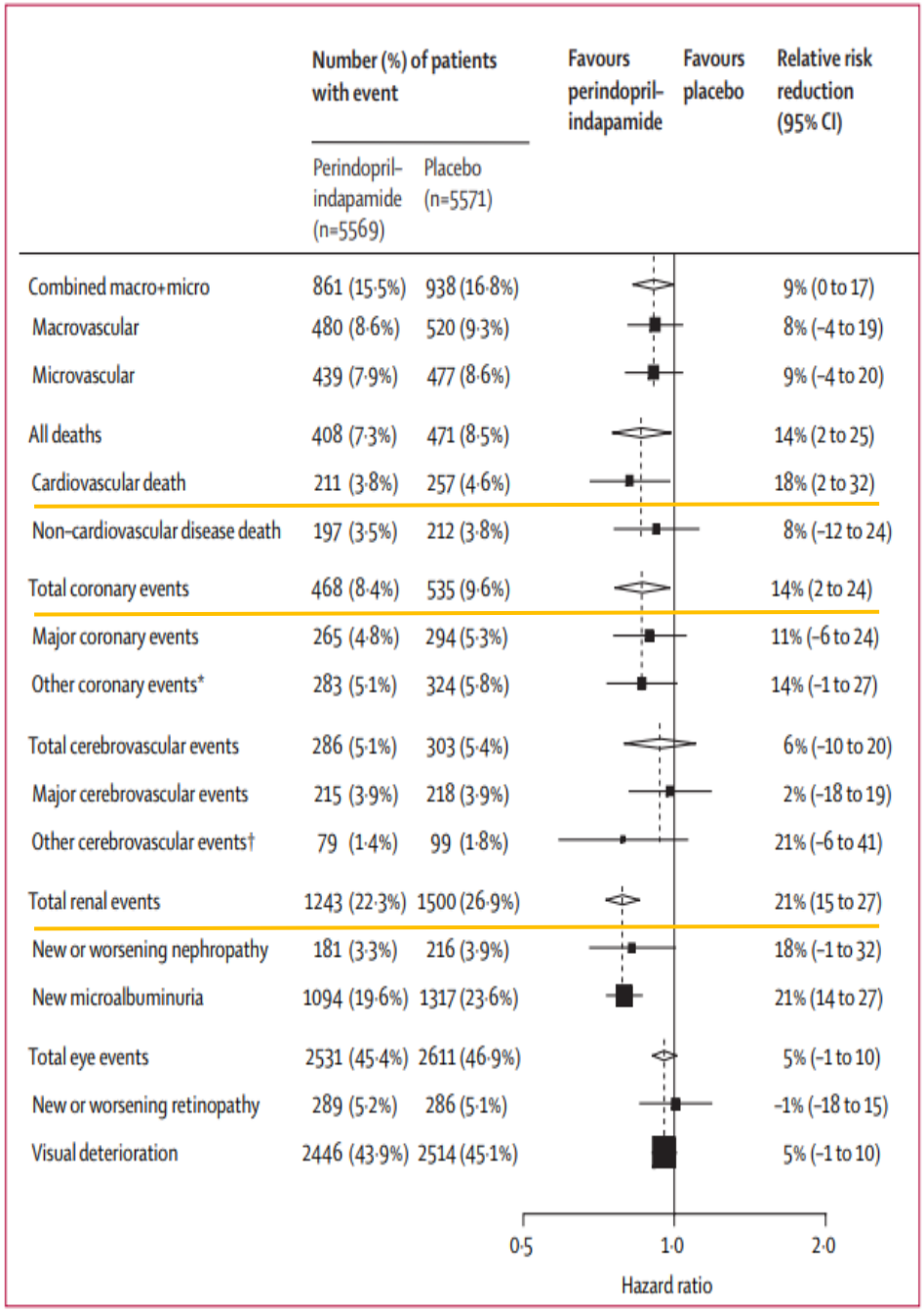


Figure 4: **Effects of study treatment on deaths, coronary events, cerebrovascular events, renal events, and eye events**

Effects of a fixed combination of perindopril and indapamide in patients with type 2 diabetes and chronic kidney disease

Hiddo J. Lambers Heerspink[1,2], Toshiharu Ninomiya[1], Vlado Perkovic[1]*, Mark Woodward[3], Sophia Zoungas[1,4], Alan Cass[1], Mark Cooper[5], Diederick E. Grobbee[6], Giuseppe Mancia[7], Carl Eric Mogensen[8], Bruce Neal[1], and John Chalmers[1], for the ADVANCE Collaborative Group†

[1]The George Institute for International Health, University of Sydney, Missenden Road, Camperdown, Sydney, NSW 2050, Australia; [2]Department of Clinical Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [3]Mount Sinai School of Medicine, New York, NY, USA; [4]School of Public Health, Monash University, Melbourne, Australia; [5]Baker IDI Heart Research Institute, Melbourne, Australia; [6]Julius Centre for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands; [7]University of Milan_Bicocca and San Gerardo Hospital, Milan, Italy; and [8]Medical Department M, Aarhus, University Hospital, Aarhus Sygehus, Aarhus C, Denmark

Received 15 December 2009; revised 30 March 2010; accepted 9 April 2010

Aims Individuals with diabetes and chronic kidney disease (CKD) are at high risk for cardiovascular disease. In these analyses of the ADVANCE trial, we assessed the effects of a fixed combination of perindopril–indapamide on renal and cardiovascular outcomes in patients with type 2 diabetes according to baseline CKD stage.

Methods and results Patients with type 2 diabetes were randomized to perindopril–indapamide (4 mg/1.25 mg) or placebo. Treatment effects on cardiovascular (cardiovascular death, myocardial infarction, or stroke) and renal outcomes were compared in subgroups defined by baseline Kidney Disease Outcome Quality Initiative CKD stage. Homogeneity in treatment effect was tested by adding interaction terms to the relevant Cox models. The study included 10 640 participants with known CKD status, of whom 6125 did not have CKD, 2482 were classified as CKD stage 1 or 2, and 2033 as CKD stage $\geq$3. The relative treatment effects on major cardiovascular events were similar across all stages of CKD, with no heterogeneity in the magnitude of the effects for any outcome. In contrast, the absolute treatment effects approximately doubled in those with CKD stage $\geq$3 when compared to those with no CKD. For every 1000 patients with CKD stage $\geq$3 treated for 5 years, active treatment prevented 12 cardiovascular events when compared with six events per 1000 patients with no CKD.

Conclusion The treatment benefits of a routine administration of a fixed combination of perindopril–indapamide to patients with type 2 diabetes on cardiovascular and renal outcomes, and death, are consistent across all stages of CKD at baseline. Absolute risk reductions are larger in patients with CKD highlighting the importance of blood pressure-lowering in this population.

European Heart Journal
doi:10.1093/eurheartj/ehq139

Effect of Low-Dose Perindopril/Indapamide on Albuminuria in Diabetes

Preterax in Albuminuria Regression: PREMIER

Carl Erik Mogensen, Giancarlo Viberti, Serge Halimi, Eberhard Ritz, Luis Ruilope, György Jermendy, Jiri Widimsky, Pinchas Sareli, Jan Taton, Juan Rull, Gürbüz Erdogan, Pieter W. De Leeuw, Arthur Ribeiro, Ramiro Sanchez, Rachid Mechmeche, John Nolan, Jana Sirotiakova, Ahmed Hamani, André Scheen, Bernhard Hess, Anton Luger, Stephen M. Thomas

Abstract—Microalbuminuria in diabetes is a risk factor for early death and an indicator for aggressive blood pressure (BP) lowering. We compared a combination of 2 mg perindopril/0.625 mg indapamide with enalapril monotherapy on albumin excretion rate (AER) in patients with type 2 diabetes, albuminuria, and hypertension in a 12-month, randomized, double-blind, parallel-group international multicenter study. Four hundred eighty-one patients with type 2 diabetes and hypertension (systolic BP ≥140 mm Hg, <180 mm Hg, diastolic BP <110 mm Hg) were randomly assigned (age 59±9 years, 77% previously treated for hypertension). Results from 457 patients (intention-to-treat analysis) were available. After a 4-week placebo period, patients with albuminuria >20 and <500 μg/min were randomly assigned to a combination of 2 mg perindopril/0.625 mg indapamide or to 10 mg daily enalapril. After week 12, doses were adjusted on the basis of BP to a maximum of 8 mg perindopril/2.5 mg indapamide or 40 mg enalapril. The main outcome measures were overnight AER and supine BP. Both treatments reduced BP. Perindopril/indapamide treatment resulted in a statistically significant higher fall in both BP (−3.0 [95% CI −5.6, −0.4], P=0.012; systolic BP −1.5 [95% CI −3.0, −0.1] diastolic BP P=0.019) and AER −42% (95% CI −50%, −33%) versus −27% (95% CI −37%, −16%) with enalapril. The greater AER reduction remained significant after adjustment for mean BP. Adverse events were similar in the 2 groups. Thus, first-line treatment with low-dose combination perindopril/indapamide induces a greater decrease in albuminuria than enalapril, partially independent of BP reduction. A BP-independent effect of the combination may increase renal protection. (***Hypertension***. 2003;41:1063-1071.)

Key Words: albuminuria ■ microalbuminuria ■ hypertension, renal ■ diabetes mellitus ■ angiotensin-converting enzyme

ORIGINAL INVESTIGATION

Effects of Blood Pressure Lowering With Perindopril and Indapamide Therapy on Dementia and Cognitive Decline in Patients With Cerebrovascular Disease

*The PROGRESS Collaborative Group**

Background: High blood pressure and stroke are associated with increased risks of dementia and cognitive impairment. This study aimed to determine whether blood pressure lowering would reduce the risks of dementia and cognitive decline among individuals with cerebrovascular disease.

Methods: The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) was a randomized, double-blind, placebo-controlled trial conducted among 6105 people with prior stroke or transient ischemic attack. Participants were assigned to either active treatment (perindopril for all participants and indapamide for those with neither an indication for nor a contraindication to a diuretic) or matching placebo(s). The primary outcomes for these analyses were dementia (using *DSM-IV* criteria) and cognitive decline (a decline of 3 or more points in the Mini-Mental State Examination score).

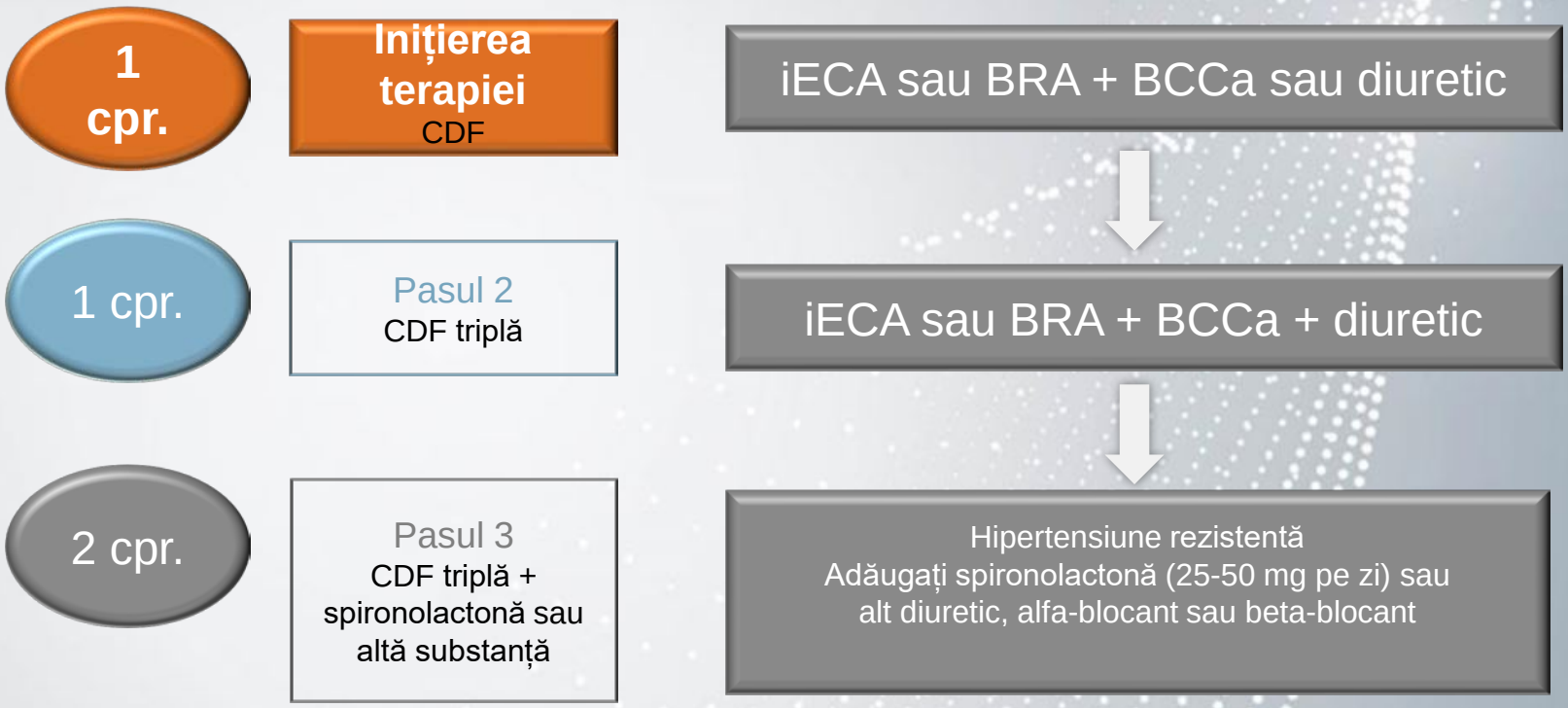
Results: During a mean follow-up of 3.9 years, dementia was documented in 193 (6.3%) of the 3051 randomized participants in the actively treated group and 217 (7.1%) of the 3054 randomized participants in the placebo group (relative risk reduction, 12% [95% confidence interval, −8% to 28%]; $P=.2$). Cognitive decline occurred in 9.1% of the actively treated group and 11.0% of the placebo group (risk reduction, 19% [95% confidence interval, 4% to 32%]; $P=.01$). The risks of the composite outcomes of dementia with recurrent stroke and of cognitive decline with recurrent stroke were reduced by 34% (95% confidence interval, 3% to 55%) ($P=.03$) and 45% (95% confidence interval, 21% to 61%) ($P<.001$), respectively, with no clear effect on either dementia or cognitive decline in the absence of recurrent stroke.

Conclusions: Active treatment was associated with reduced risks of dementia and cognitive decline associated with recurrent stroke. These findings further support the recommendation that blood pressure lowering with perindopril and indapamide therapy be considered for all patients with cerebrovascular disease.

Arch Intern Med. 2003;163:1069-1075

Am inlocuit Enalapril si Indapamida cu CoPrenessa 8/2.5mg

Terapia cu CDF reprezintă baza tratamentului pentru controlul hipertensiunii arteriale



Algoritmul de bază al tratamentului este adecvat pentru pacienții cu leziuni de organ țintă de hipertensiune, boli cerebrovasculare, diabet sau boală arterială periferică.

CDF-combinație în doză fixă, iECA-inhibitori ai enzimei de conversie ai angiotensiei, BRA – Blocanți ai receptorilor de angiotensină II, BCCa – blocant al canalelor de calciu

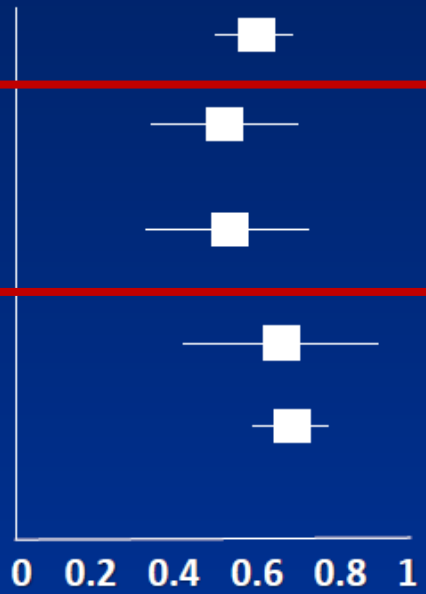
Williams B, Mancia G, Spiering W et.al. ESC Scientific Document Group; 2018 ESC/ESH Guidelines for the management of arterial hypertension, European Heart Journal 2018; 39 (33): 3021–104.

European Heart Journal
doi:10.1093/eurheartj/eht295

CLINICAL RESEARCH
Prevention and epidemiology

Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences

	No. of Studies	No. of Participants	Proportion (95% CI)
Adherence to any CVD Medication	34	1.230.382	0,60 (0,52-0,68)
Adherence to STATINS	12	771.323	0,54 (0,41-0,67)
Adherence to ANTIHYPERTENSIVES	11	363.819	0,54 (0,42-0,77)
Adherence to ASPIRIN	2	11.068	0,70 (0,49-0,91)
Adherence to ANTIDIABETIC AGENTS	2	1112	0,69 (0,59-0,78)



9% dintre decesele din U.E. se datorează lipsei de aderență la tratament. Aderența crescută la tratamentul cardiovascular poate duce la reducerea cu peste 20% a riscului unui eveniment cardiovascular.

Chowdhury R et al. EHJ, 2013;34(38):2940-8.

2018 ESC/ESH Guidelines for the management of arterial hypertension

Lipsa de ADERENTA la tratament: cauza majora pt neatingerea tintelor terapeutice!

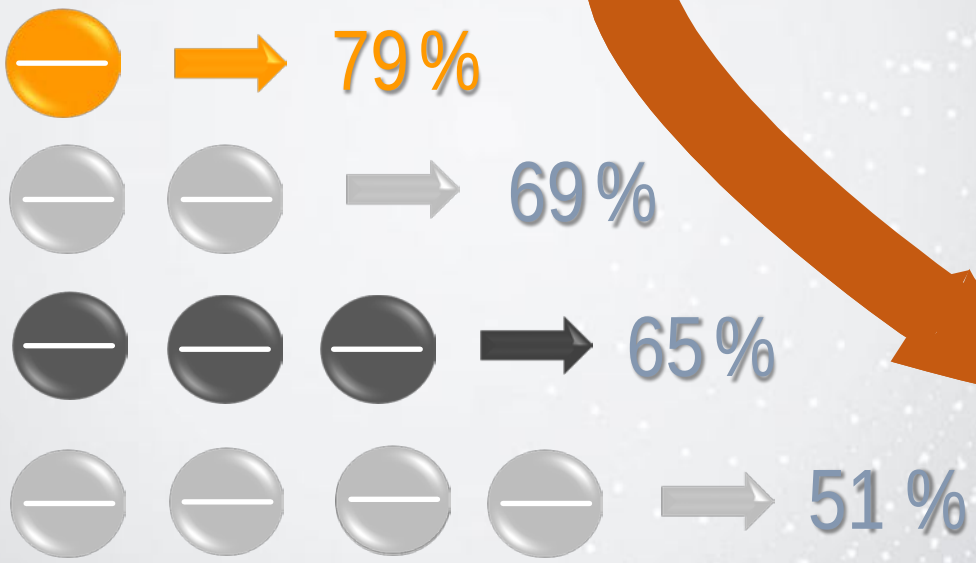
Detecting poor adherence to drug therapy

- A strong emphasis on the **importance of evaluating treatment adherence** as a major cause of poor BP control.

Mancia G et al, *European Heart Journal* (2018) 39, 3021–3104

Ajută pacientul să fie mai aderent la terapie prin simplificarea tratamentului

Cea mai bună aderență este atinsă prin tratamentul administrat 1x zilnic

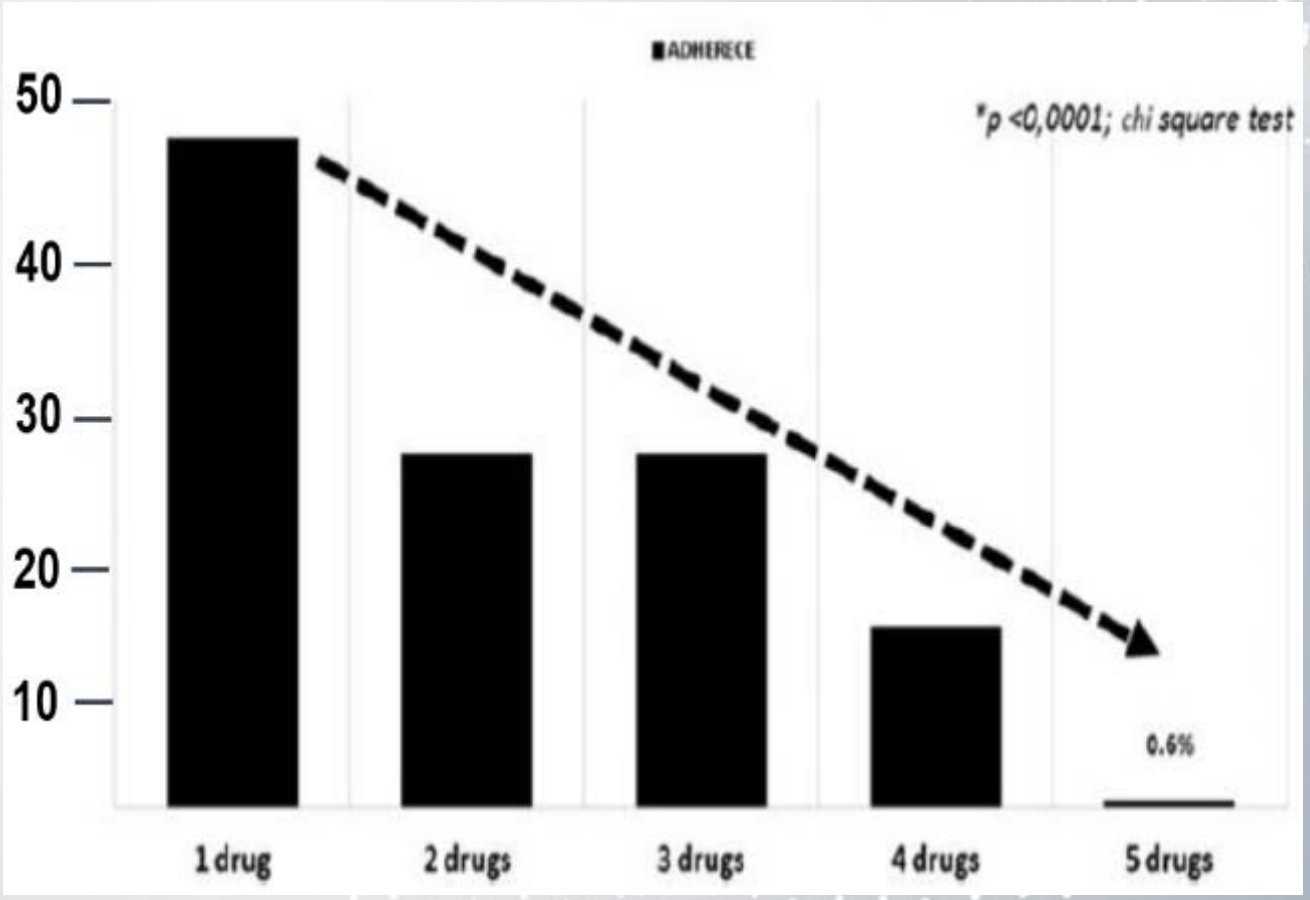


Cantitatea de tablete consumată într-un an

Un număr mai mare de tablete scade aderența.

Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther. 2001 Aug;23(8):1296–310.

1 din 2 pacienti hipertensivi sunt non-aderenti la tratament



SEPHAR III - Dorobantu M et al, *Journal of Hypertension* 2017, 35:000–000.

IECA si tiazidele nu sunt la fel!
Dar statinele?

Comparative effectiveness of statins on non-high density lipoprotein cholesterol in people with diabetes and at risk of cardiovascular disease: systematic review and network meta-analysis

Alexander Hodkinson,[1,9] Dialechti Tsimpida,[1,2,3] Evangelos Kontopantelis,[1,2,4] Martin K Rutter,[5,6] Mamas A Mamas,[1,7,8] Maria Panagioti[1,9]

Table 1 | Statin dosing and American College of Cardiology/American Heart Association, European Society of Cardiology, and National Institute for Health and Care Excellence classification of intensity according to percentage reduction in low density lipoprotein cholesterol (LDL-C)

	Total daily dose, mg		
Statin	Low intensity (LDL-C reduced by 20-30%)	Moderate intensity (LDL-C reduced by 31-39%)	High intensity (LDL-C reduced by ≥40%)
Atorvastatin	NA	10-20	40-80
Fluvastatin	20-40	80	NA
Lovastatin	20	40-80	NA
Pitavastatin	NA	1-4	NA
Pravastatin	10-20	40-80	NA
Rosuvastatin	NA	5-10	20-40
Simvastatin	10	20-40	80

NA=no classification available from any guideline

thebmj | *BMJ* 2022;376:e067731 | doi: 10.1136/bmj-2021-067731

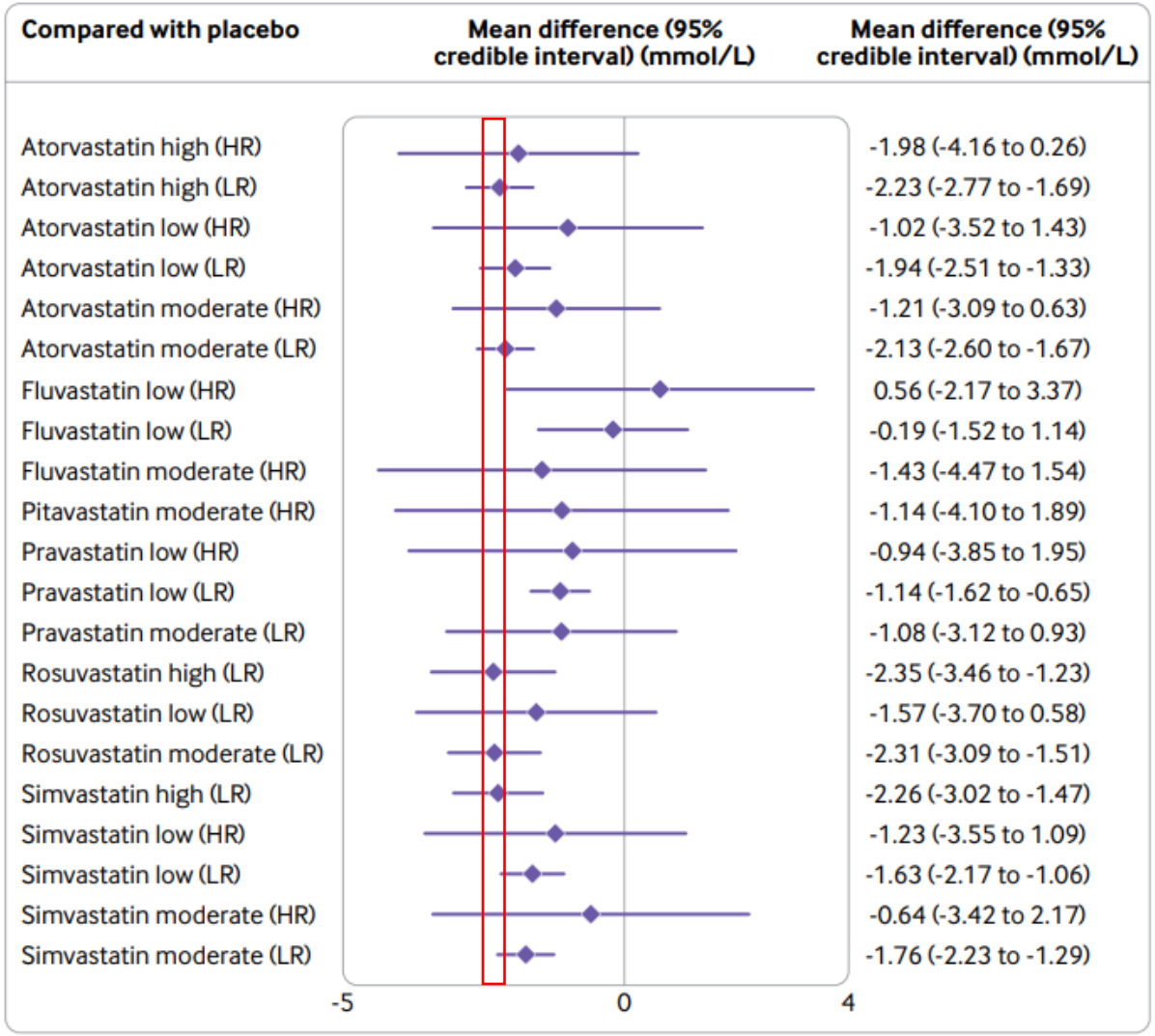


Fig 5 | Network of available comparisons between statin intensities for non-high density lipoprotein cholesterol adjusted for patient risk, with forest plot of network effect sizes compared with placebo. Size of node is proportional to number of trial participants, and thickness of line connecting nodes is proportional to number of trial participants randomised in trials directly comparing the two treatments. Patient risk is classified as high (HR) and low to moderate (LR)

Choosing statins: a review to guide clinical practice

Table 2. Maximum recommended doses of statins in adults with chronic kidney disease according to estimated glomerular filtration rate (eGFR)

Statin	eGFR mL/min/1.73 m²				
	60-89	45-59	30-44	15-29	<15
Atorvastatin					
Lovastatin				20	20
Pitavastatin		2	2	2	2
Pravastatin		10	10	10	10
Rosuvastatin				10	10
Simvastatin				10	10
Fluvastatin					
Simvastatin/ ezetimibe		20/10	20/10	20/10	20 /10

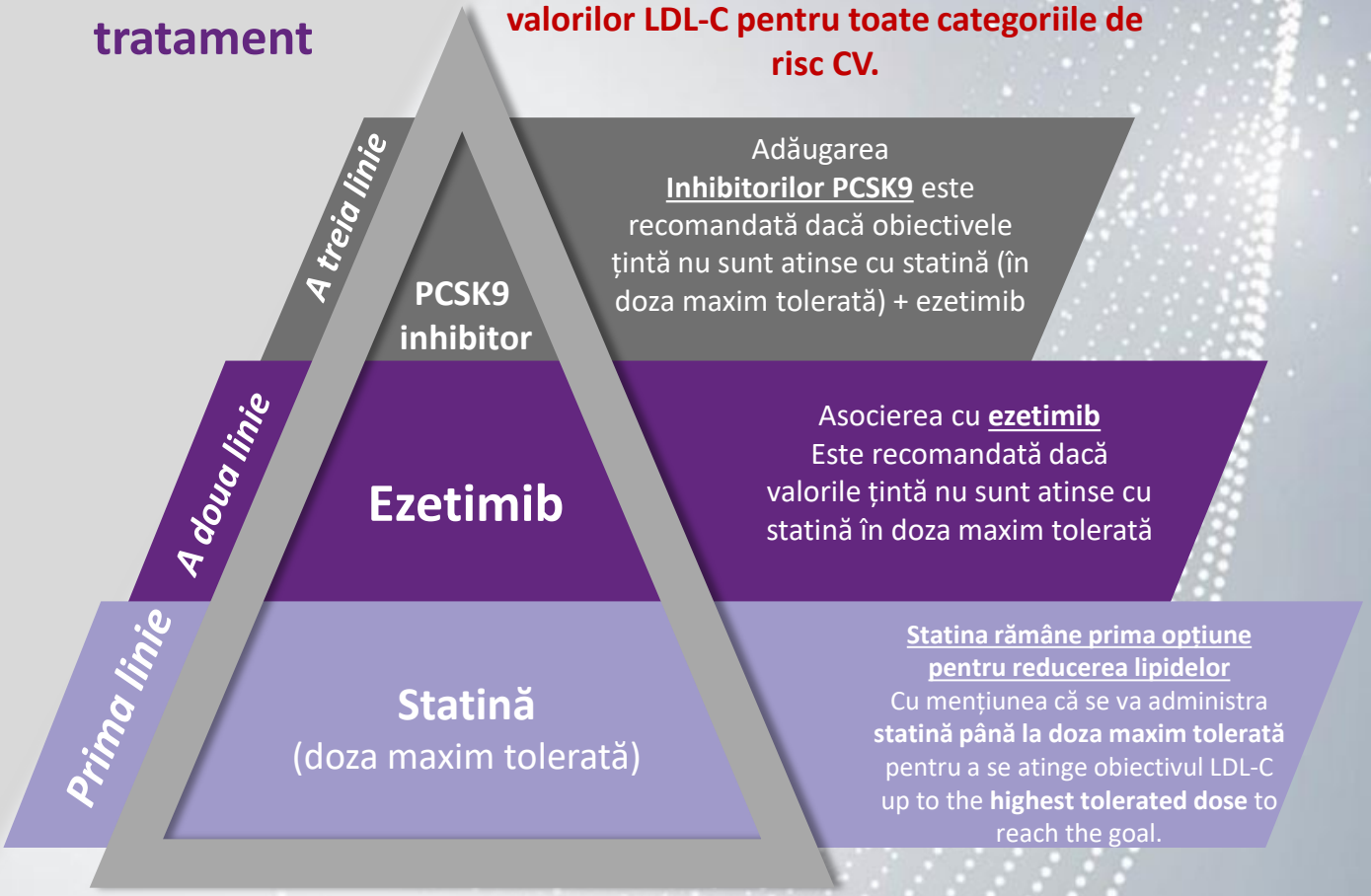
No dose adjustment necessary.

Maximum dose (mg).

Arch Endocrinol Metab. 2020;64/6

Recomandări de tratament

Se recomandă reducerea semnificativă a valorilor LDL-C pentru toate categoriile de risc CV.



CV - cardiovascular, LDL-C - LDL-colesterol

Reference: Mach F, Baigent C, Catapano AL et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Euro Heart Jour. 2019; 00: 1-78. doi:10.1093/eurheartj/ehz455.

Adăugarea de ezetimib la tratamentul cu statină oferă o reducere suplimentară a LDL-C și protecție CV adițională

Medical background

Disease basics

statină

Reduce sinteza colesterolului în ficat

ezetimib

Reduce colesterolul prin inhibarea **absorbției intestinale** a colesterolului

Ezetimib + statină → mecanism dual de acțiune

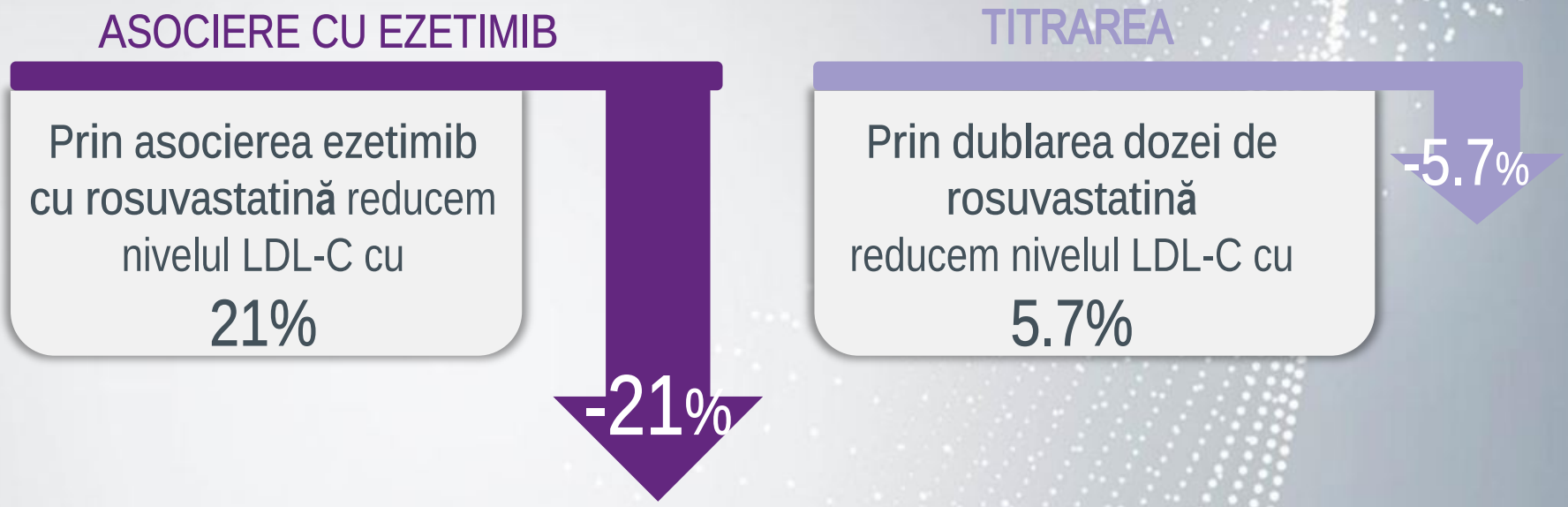
Combinând ezetimib cu statină, prin mecanismele distincte de acțiune, obținem o **reducere a colesterolului complementar**, astfel **o mai mare reducere a colesterolului** în comparație cu moleculele administrate separat

Reducere adițională a LDL-C cu 15–20%

CV-cardiovascular

References: 1. Hammersley D, Signy M. Ezetimibe: an update on its clinical usefulness in specific patient groups. Ther Adv Chronic Dis 2017, 8(1) 4-11. 2. Reiner Ž. Combined therapy in the treatment of dyslipidemia. Fundamental & Clinical Pharmacology 2010; 24: 19–28.

Prin asocierea cu ezetimib, reducerea LDL-c este semnificativ mai mare față de dublarea dozei de statină



Asocierea dintre EZETIMIB **și** ROSUV**ASTATINĂ** asigură reducerea semnificativă a LDL-C comparativ cu titrarea ascendentă a RSV.

EZE – ezetimib,
LDL-C – LDL colesterol, RSV - rosuvastatină

KRKA

Atherosclerosis 223 (2012) 251–261

Contents lists available at SciVerse ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review

Lipid-altering efficacy of ezetimibe plus statin and statin monotherapy and identification of factors associated with treatment response: A pooled analysis of over 21,000 subjects from 27 clinical trials

Doralisa Morrone [a,*], William S. Weintraub [a], Peter P. Toth [b,c], Mary E. Hanson [d], Robert S. Lowe [d], Jianxin Lin [d], Arvind K. Shah [d], Andrew M. Tershakovec [d]

[a] *Cardiology Section, Christiana Care Health System, Newark, DE, United States*
[b] *CGH Medical Center, Sterling, IL, United States*
[c] *University of Illinois College of Medicine, Peoria, IL, United States*
[d] *Merck Sharp & Dohme Corp., Whitehouse Station, NJ, United States*

Table 3A

Treatment effects of statins and statins + ezetimibe in the overall population. Percent change from baseline in lipids, lipoproteins, and hs-CRP.[a]

Parameter	Statin ($n = 10,055$)	Statin + EZE ($n = 11,225$)	Treatment difference[b,c]	p-Value
LDL-C	−23.6	−38.7	−15.1	<0.0001
non-HDL-C	−21.4	−35.0	−13.5	<0.0001
Total C	−17.0	−27.1	−10.1	<0.0001
Triglycerides[d,e]	−15.4	−19.9	−4.7	<0.0001
Apo B	−18.1	−28.9	−10.8	<0.0001
HDL-C	2.1	3.7	1.6	<0.0001
Apo A-I	0.0	0.8	0.8	<0.0001
Total-C/HDL-C	−17.8	−28.6	−10.9	<0.0001
LDL-C/HDL-C	−24.3	−39.8	−15.5	<0.0001
non-HDL-C/HDL-C	−21.9	−36.0	−14.1	<0.0001
Apo B/Apo A-I	−16.5	−28.3	−11.8	<0.0001
hs-CRP[f]	−8.2	−16.7	−8.6	<0.0001

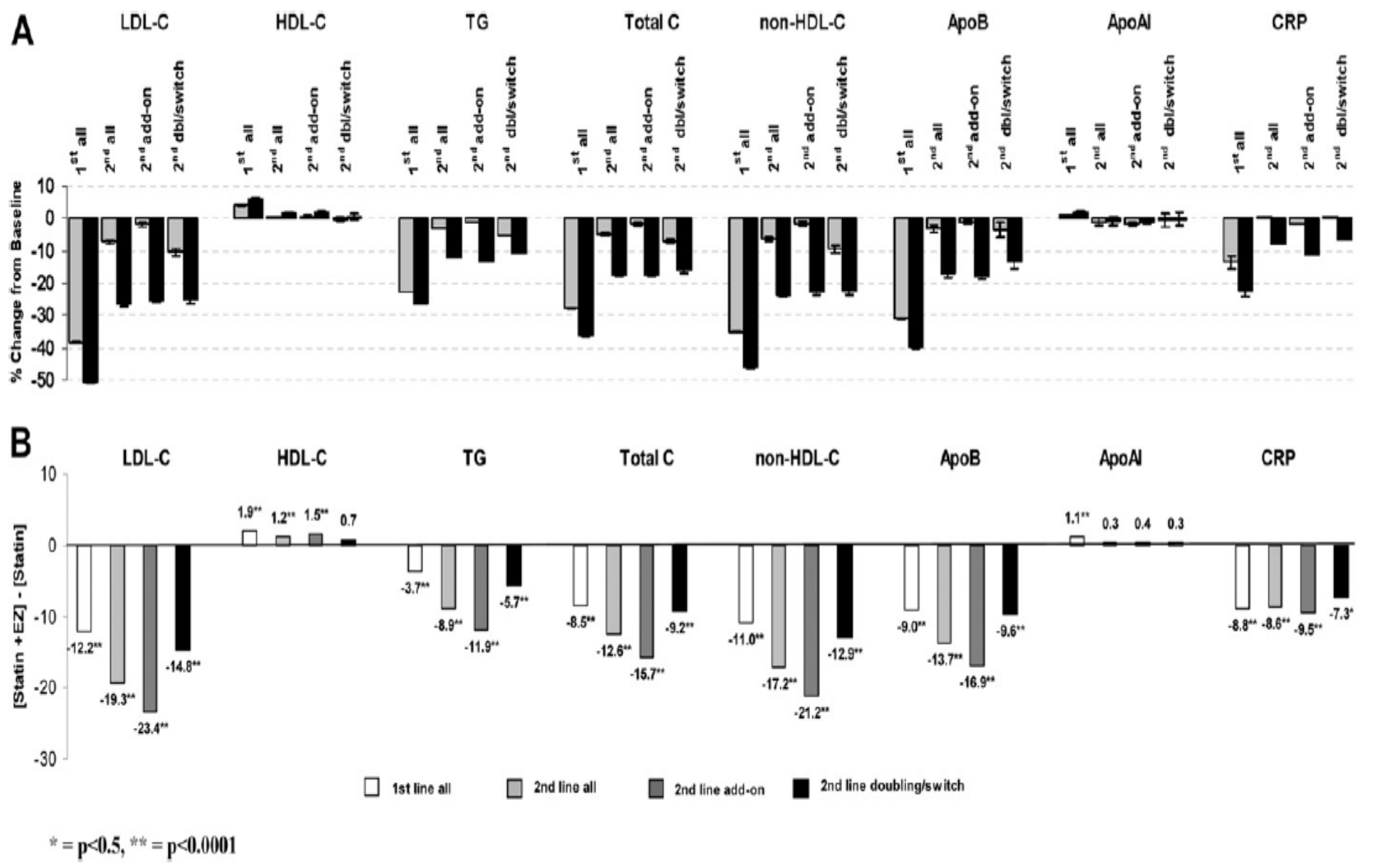


Fig. 1. (A) Percent change from baseline in lipids, lipoproteins, and hs-CRP – by first and second line study design. (B) Percent change from baseline differences between statin + ezetimibe and statin alone.

Pe lângă reducerea nivelului LDL-c, terapia combinată cu ezetimib și statină asigură o protecție cardiovasculară sporită

Terapia combinată cu ezetimib și statină

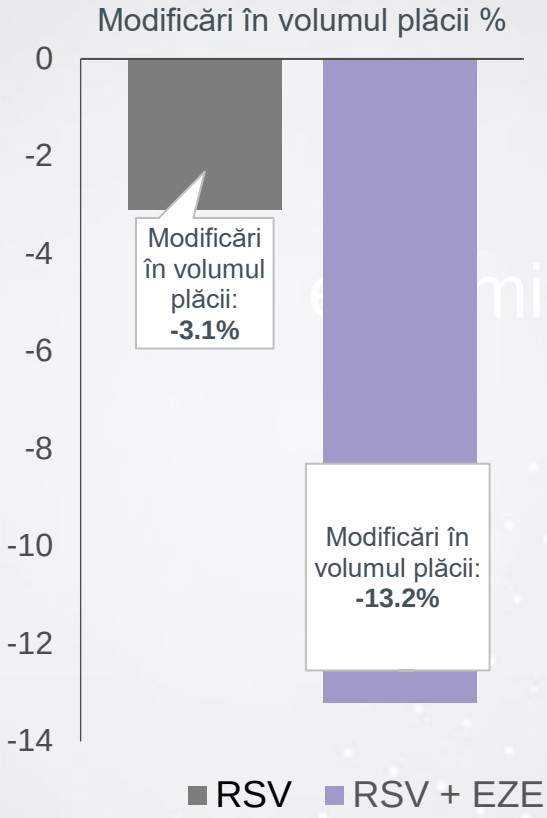
Reducere adițională a nivelului LDL-C cu 15-20%

Reducerea riscului cardiovascular fiind dovedită clinic

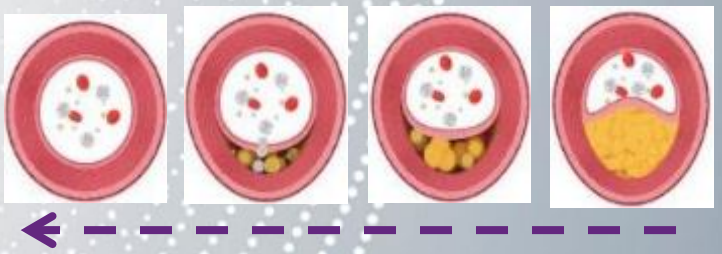
LDL-C – LDL colesterol, CV – cardiovascular

References: 1. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. EHJ 2016; 37(29): 2315-81. 2. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. EHJ 2016; 37(39): 2999-3058.

Efecte benefice asupra plăcii de aterom



Adăugarea de **ezetimib** duce la o regresie mai mare a plăcii de aterom.



Regresia plăcii de aterom

Dozele utiliate în studiu:
RSV – 5 mg; EZE – 10 mg

Abrevieri:
RSV – rosuvastatină, EZE – ezetimib

Reference: Masuda et.al. Effect of Combination therapy of ezetimibe and rosuvastatin on regression of coronary atherosclerosis in patients with coronary artery disease. Int Heart J 2015; 56: 278-285.

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 66, NO. 5, 2015

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jacc.2015.05.065

ORIGINAL INVESTIGATIONS

Impact of Dual Lipid-Lowering Strategy With Ezetimibe and Atorvastatin on Coronary Plaque Regression in Patients With Percutaneous Coronary Intervention

The Multicenter Randomized Controlled PRECISE-IVUS Trial

FIGURE 3 Plaque Progression/Regression

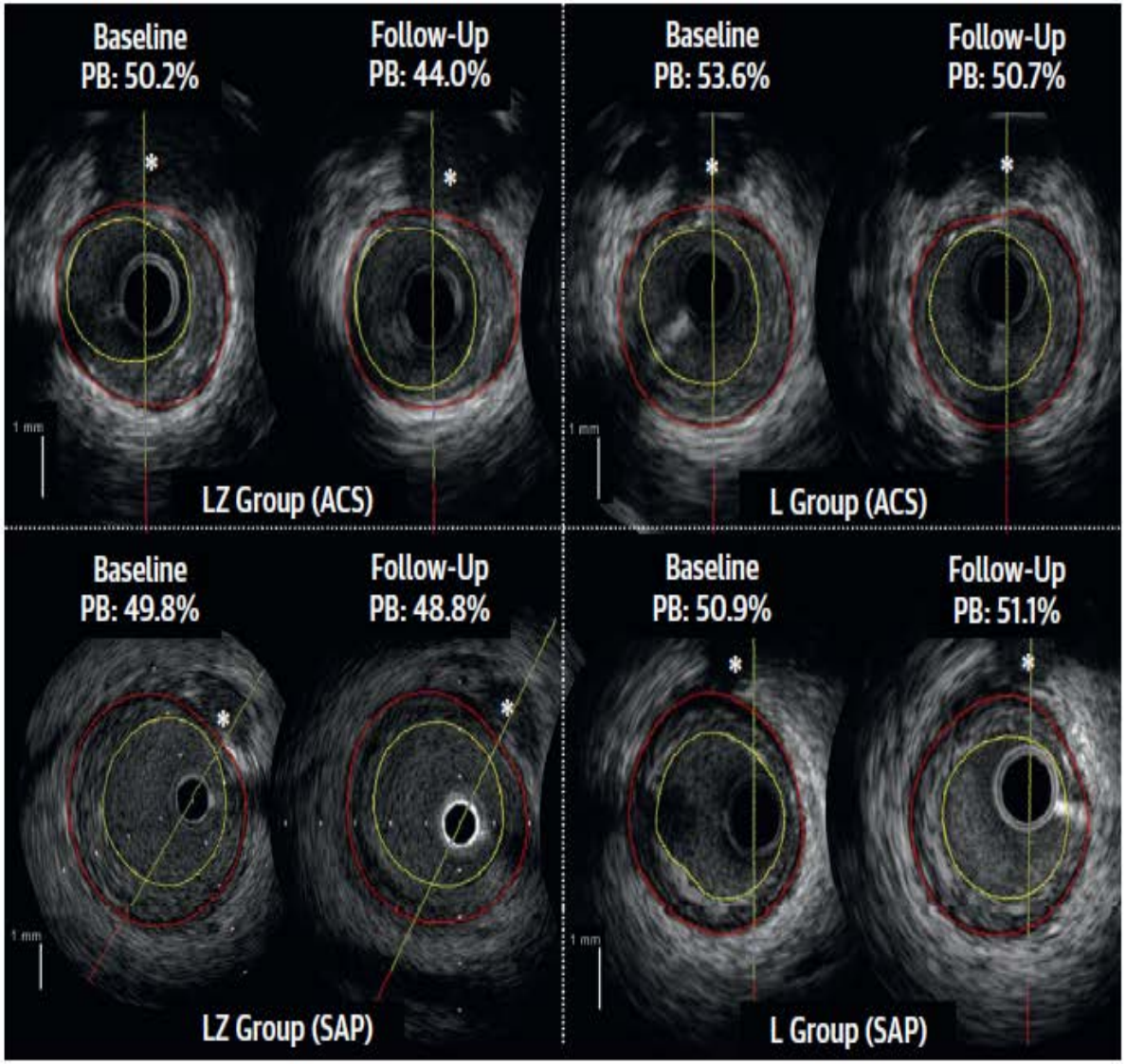
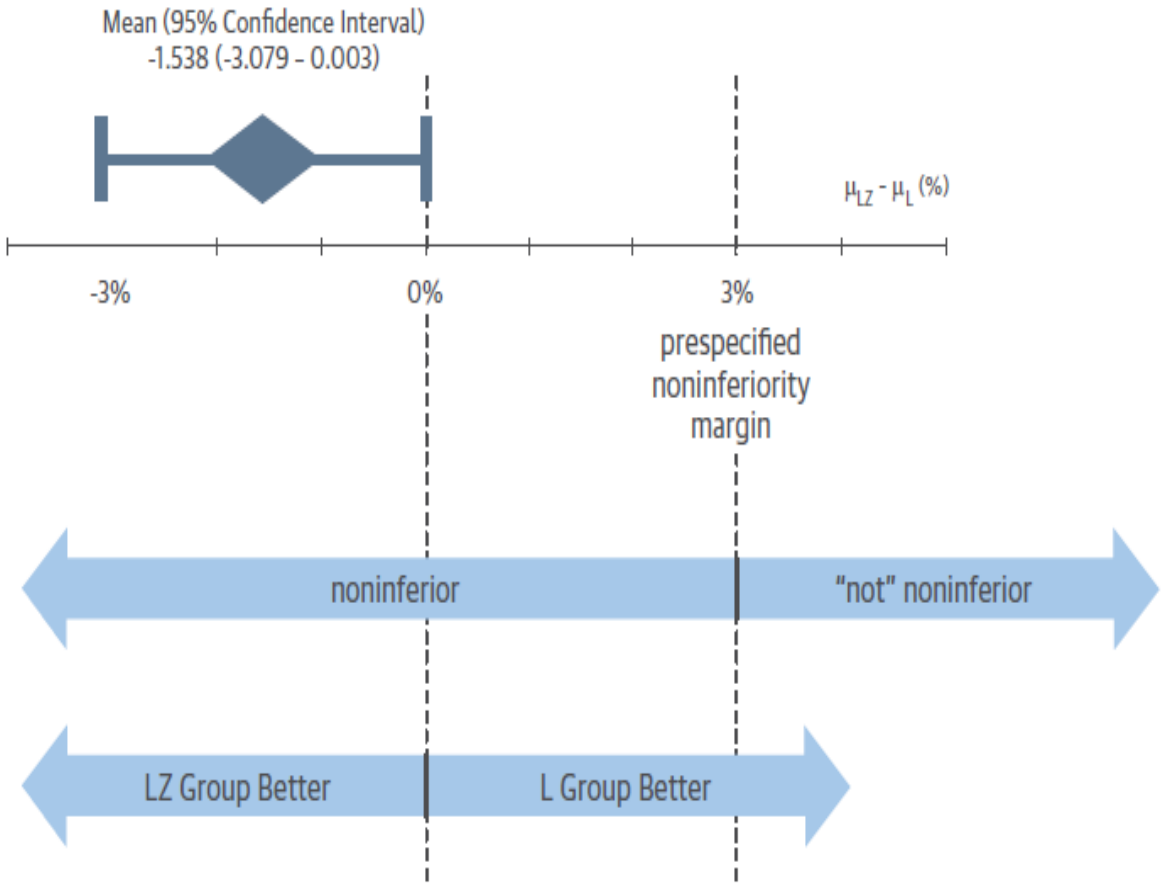


FIGURE 2 Primary Endpoint: Absolute Change in PAV



The atorvastatin/ezetimibe (LZ) group was noninferior to the atorvastatin-alone (L) group in terms of the primary endpoint, which was the absolute change in percent atheroma volume (PAV). $\mu_{LZ} - \mu_L$ indicates the difference of drug effects on absolute change in PAV, where μ_{LZ} represents the absolute change in PAV in the LZ group and μ_L represents that of the L group.

CONCLUSIONS

Among Japanese patients who underwent PCI, aggressive lipid-lowering with dual inhibition of cholesterol synthesis and absorption produced stronger coronary plaque regression compared with sole inhibition of the cholesterol biosynthetic pathway. Combination therapy with statin plus ezetimibe might thus be a promising lipid-lowering option for high-risk patients.

Circulation

ORIGINAL RESEARCH ARTICLE

Benefit of Adding Ezetimibe to Statin Therapy on Cardiovascular Outcomes and Safety in Patients With Versus Without Diabetes Mellitus

Results From IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)

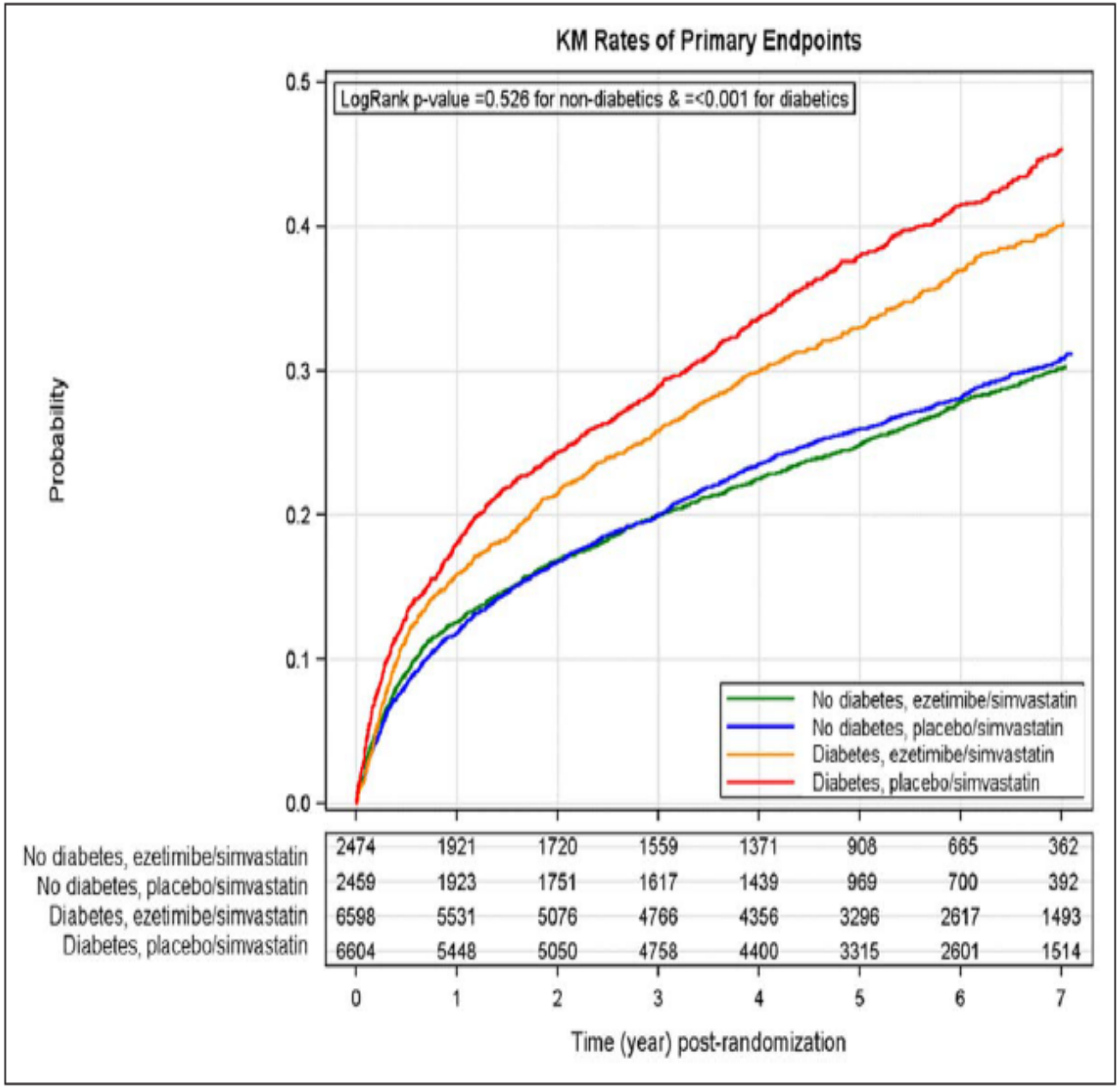
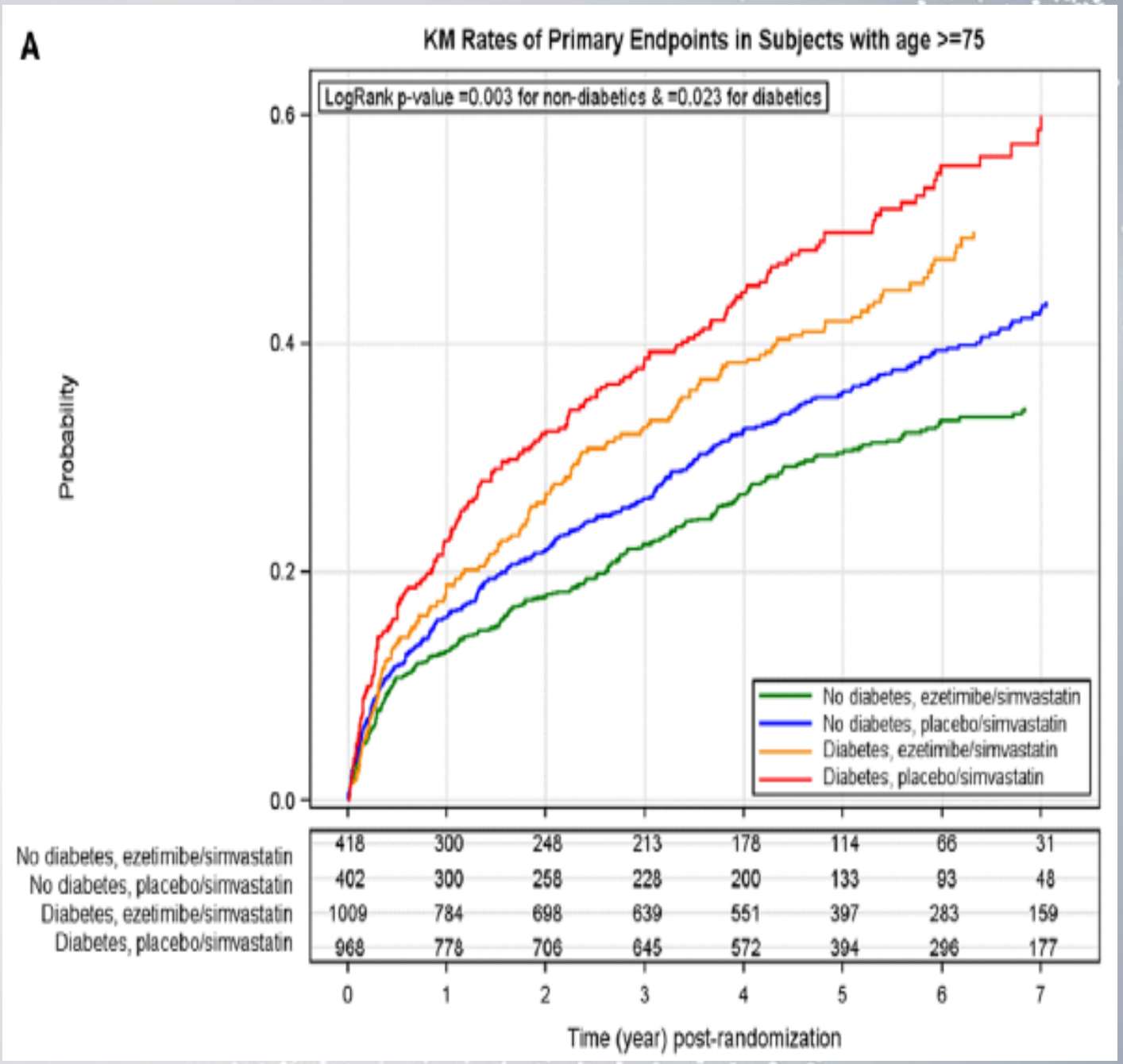


Figure 1. Kaplan–Meier curves for the primary efficacy end point.


A
KM Rates of Primary Endpoints in Subjects with age >=75
LogRank p-value =0.003 for non-diabetics & =0.023 for diabetics
Probability
0.6
0.4
0.2
0.0
No diabetes, ezetimibe/simvastatin
No diabetes, placebo/simvastatin
Diabetes, ezetimibe/simvastatin
Diabetes, placebo/simvastatin
No diabetes, ezetimibe/simvastatin 418 300 248 213 178 114 66 31
No diabetes, placebo/simvastatin 402 300 258 228 200 133 93 48
Diabetes, ezetimibe/simvastatin 1009 784 698 639 551 397 283 159
Diabetes, placebo/simvastatin 968 778 706 645 572 394 296 177
0 1 2 3 4 5 6 7
Time (year) post-randomization

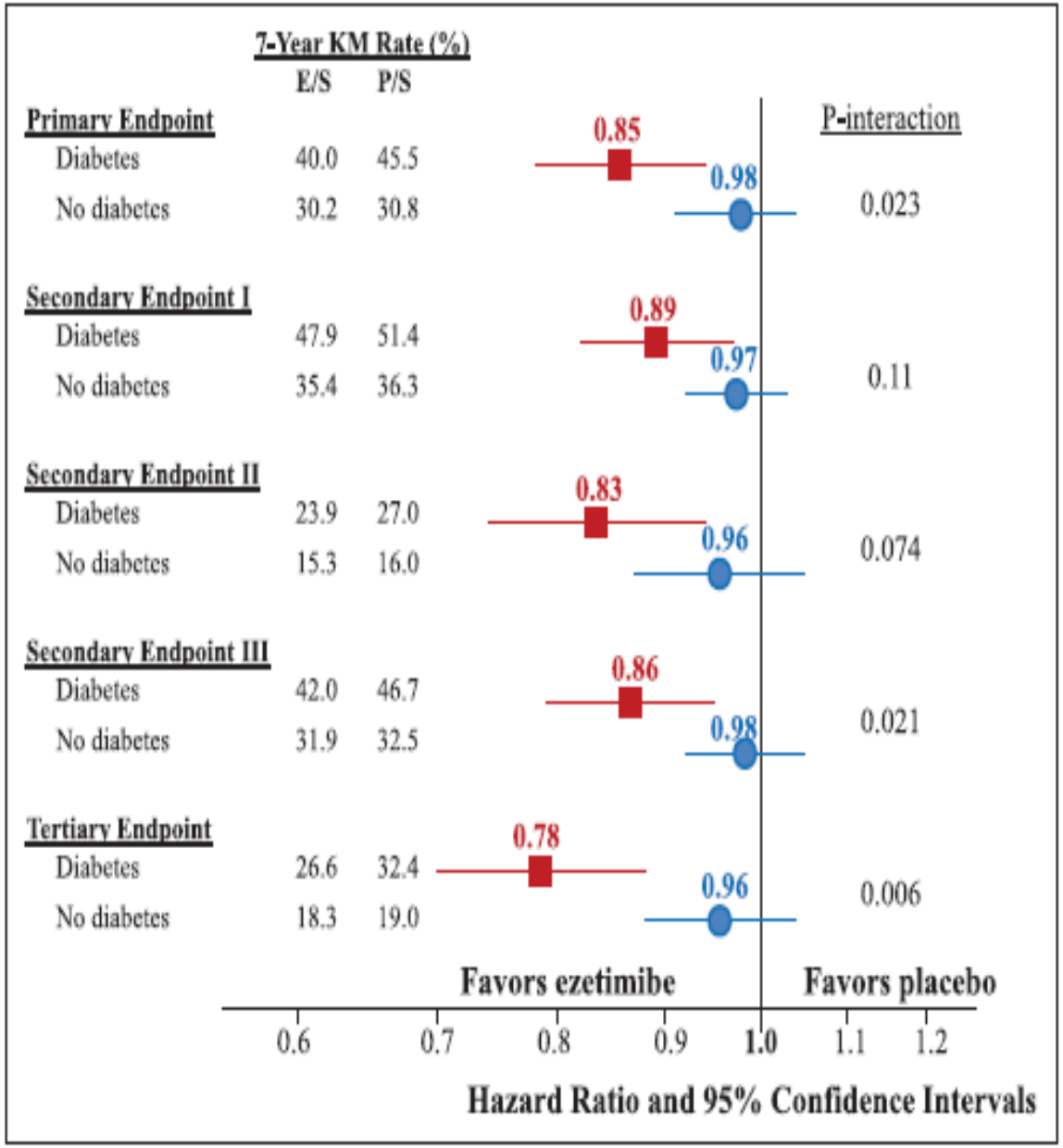


Figure 2. Composite efficacy outcomes stratified by treatment and diabetes mellitus status.
Hazard ratios and 95% confidence intervals are shown for the comparison of ezetimibe/simvastatin (E/S) versus placebo/simvastatin (P/S) in patients with (red) and without (blue) diabetes mellitus. See text and the footnotes to Table 2 for definitions of the composite endpoints.

CONCLUSIONS

In the IMPROVE-IT of 18144 patients with ACS and LDL-C 50 to 125 mg/dL, the benefit of adding ezetimibe to statin appeared to be enhanced among patients with DM, with no adverse effect in safety. These findings support the use of intensive, combination lipid-lowering therapy in patients with DM to optimize cardiovascular outcomes, as recommended by the American Association of Clinical Endocrinologists and the American College of Endocrinology.[33]

Study of Heart and Renal Protection (SHARP): Randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease

SHARP Collaborative Group

Background Lowering low-density lipoprotein (LDL) cholesterol with statin therapy has been shown to reduce the incidence of atherosclerotic events in many types of patient, but it remains uncertain whether it is of net benefit among people with chronic kidney disease (CKD).

Methods Patients with advanced CKD (blood creatinine ≥1.7 mg/dL [≥ 150 μmol/L] in men or ≥1.5 mg/dL [≥ 130 μmol/L] in women) with no known history of myocardial infarction or coronary revascularization were randomized in a ratio of 4:4:1 to ezetimibe 10 mg plus simvastatin 20 mg daily versus matching placebo versus simvastatin 20 mg daily (with the latter arm rerandomized at 1 year to ezetimibe 10 mg plus simvastatin 20 mg daily vs placebo). The key outcome will be *major atherosclerotic events*, defined as the combination of myocardial infarction, coronary death, ischemic stroke, or any revascularization procedure.

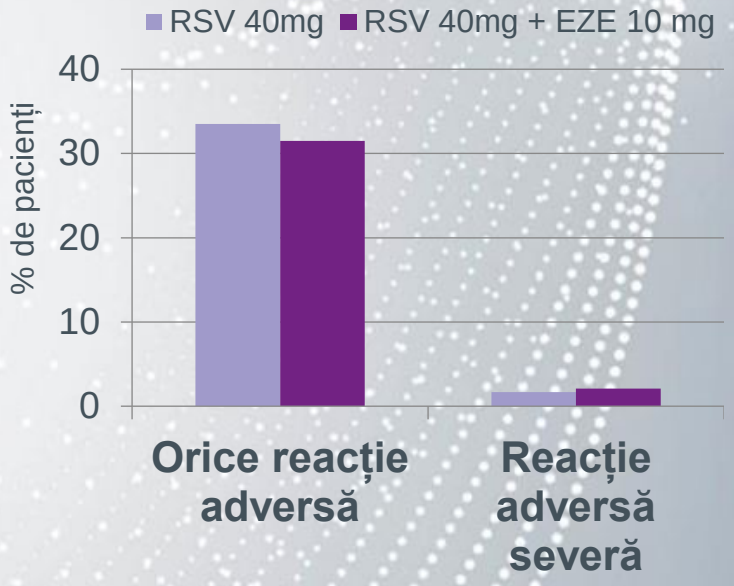
Results A total of 9,438 CKD patients were randomized, of whom 3,056 were on dialysis. Mean age was 61 years, two thirds were male, one fifth had diabetes mellitus, and one sixth had vascular disease. Compared with either placebo or simvastatin alone, allocation to ezetimibe plus simvastatin was not associated with any excess of myopathy, hepatic toxicity, or biliary complications during the first year of follow-up. Compared with placebo, allocation to ezetimibe 10 mg plus simvastatin 20 mg daily yielded average LDL cholesterol differences of 43 mg/dL (1.10 mmol/L) at 1 year and 33 mg/dL (0.85 mmol/L) at 2.5 years. Follow-up is scheduled to continue until August 2010, when all patients will have been followed for at least 4 years.

Conclusions SHARP should provide evidence about the efficacy and safety of lowering LDL cholesterol with the combination of ezetimibe and simvastatin among a wide range of patients with CKD. (Am Heart J 2010;160:785-794.e10.)

Profilul de siguranță al combinației RSV + EZE este similar cu RSV în monoterapie

Asocierea de **EZE** cu **RSV** a asigurat o **eficacitate mai bună a terapiei hipolipeminate** și **atingerea țintelor lipidice** cu un **profil de siguranță similar cu cel al rosuvastatinei în monoterapie.**

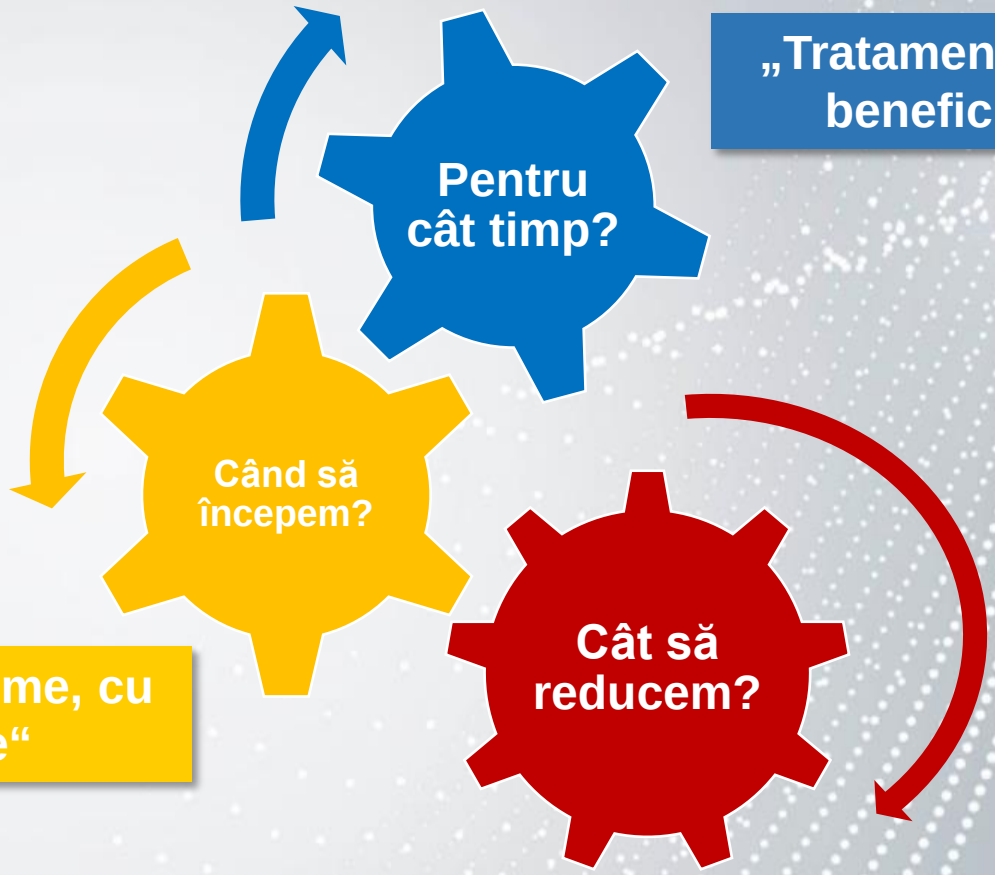
- ✓ Ambele tratamente au fost **bine tolerate.**
- ✓ **Frecvență și tip similar a reacțiilor adverse** între tratamente**.**



Abrevieri:
EZE – ezetimib, RSV – rosuvastatină

Reference: Ballantyne CM et al. Efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe in patients at high risk of CVD. Am J Cardiol 2007; 99(5): 673-80.

Am inlocuit Simvastatina cu CoRoswera (Rosuvastatina+Ezetimib) 40/10mg/zi



„Tratament îndelungat, beneficii sporite“

„Cu cât mai devreme, cu atât mai bine“

„Cu cât nivelul este mai scăzut nivelul LDL-C, cu atât mai bine“

Acționează preventiv!

Diagnosticarea, conștientizarea și **managementul factorilor de risc** trebuie îmbunătățite.

Astfel se **asigură prevenția la un nivel optim**, se **evită consecințele date de afecțiune** și se **îmbunătățește calitatea vieții pacienților.**

»Un om este la fel de bătrân ca și arterele sale«

Dr. Thomas Sydenham, British physician (1624-1689)


Va multumesc pentru atentie!