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VIATRIS

Renal Safety Issues in Dyslipidemia Treatment : Why is it important ?

Duk-Woo Park, MD
Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

CONTENTS

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Importance of considering renal safety

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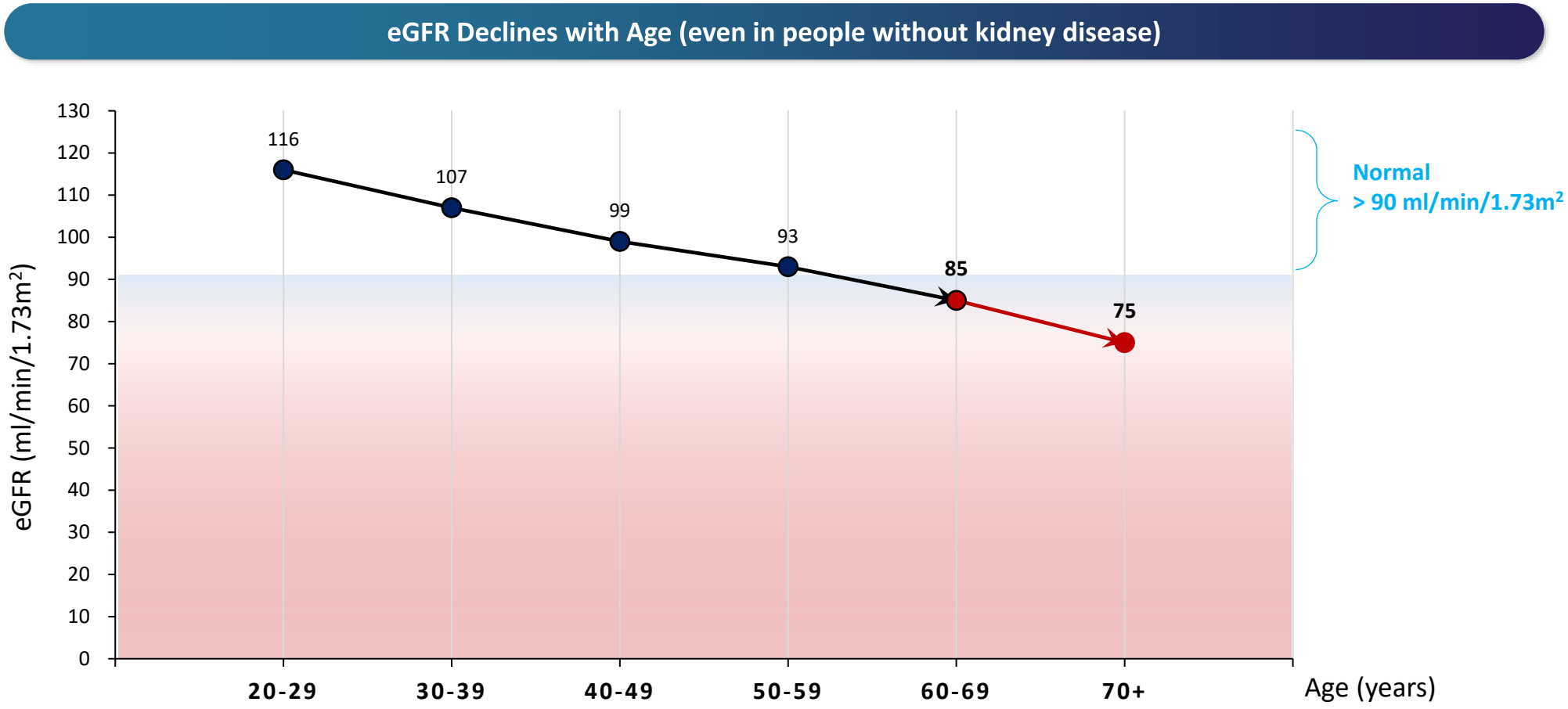
Kidney function declines with aging



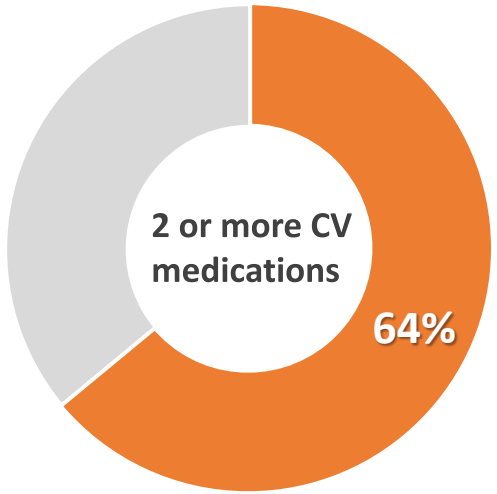
eGFR, estimated glomerular filtration rate

Ref. National Kidney Foundation. Accessed March 11, 2024 at https://www.kidney.org/sites/default/files/11-10-1813_estimated_glomerular_filtration_rate.pdf

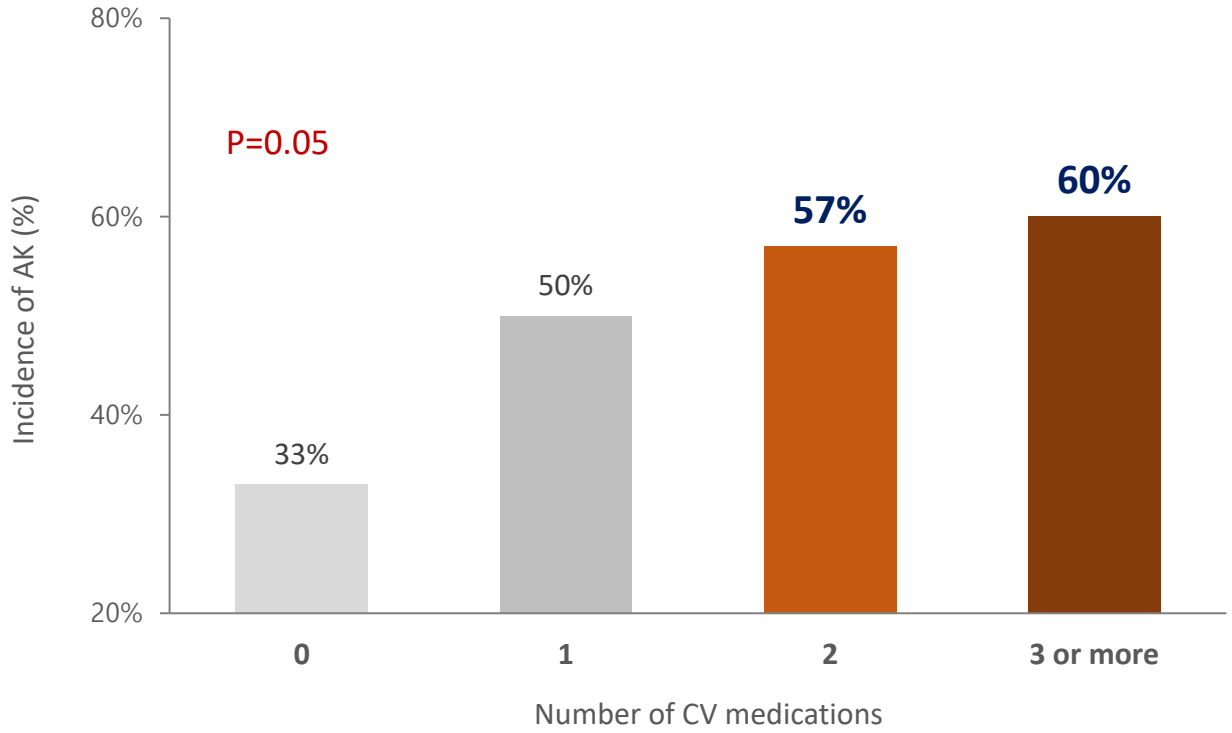
Cumulative CV polypharmacy is associated with the risk of acute kidney injury in elderly patients

An observational study (Taiwan)
152 in-patients older than 60 years
Number of CV drugs before admission : Mean 2.2±1.8 (range 0-8)

Prevalence of CV polypharmacy on admission



Incidence of AKI according to number of preadmission CV medications



CV, cardiovascular; **AKI**, acute kidney injury

Ref. Chao C, et al. Cumulative Cardiovascular Polypharmacy Is Associated With the Risk of Acute Kidney Injury in Elderly Patients. Medicine 2015;94:e1251.

Each additional CV medication increased the risk for AKI by 30%

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Factors associated with development of AKI (multiple regression analysis)

Models	Variables	OR (95% CI)	p-value
Model 1	Diabetes mellitus	1.93 (0.89-4.18)	0.1
	1 type of CV medication (vs none)	1.63 (0.65-7.56)	0.2
	2 types of CV medication (vs none)	4.74 (1.14-11.6)	0.03
	>2 types of CV medication (vs none)	5.92 (1.31-12.4)	0.02
Model 2	Diabetes mellitus	2.16 (1.02-4.58)	0.04
	CV medications (per 1 type increase)	**1.30** (1.03-1.64)	0.03
Model 3	Diabetes mellitus	2.19 (1.03-4.64)	0.04
	CV polypharmacy	**2.58** (1.15-5.76)	0.02

Model 1 included variables from demographic data, all comorbidities, admission diagnosis, laboratory profile, and CV medication usage status (in quintiles).
Model 2 included the same variables as Model 1. But considered CV medication usage status as a continuous variable.
Model 3 included the same variables as Model 1. But considered CV polypharmacy as a binary variable.

CV, cardiovascular; **AKI**, acute kidney injury; **OR**, odds ratio; **CI**, confidence interval

Ref. Chao C, et al. Cumulative Cardiovascular Polypharmacy Is Associated With the Risk of Acute Kidney Injury in Elderly Patients. Medicine 2015;94:e1251.

Risk of kidney dysfunction from polypharmacy among Korean older patients

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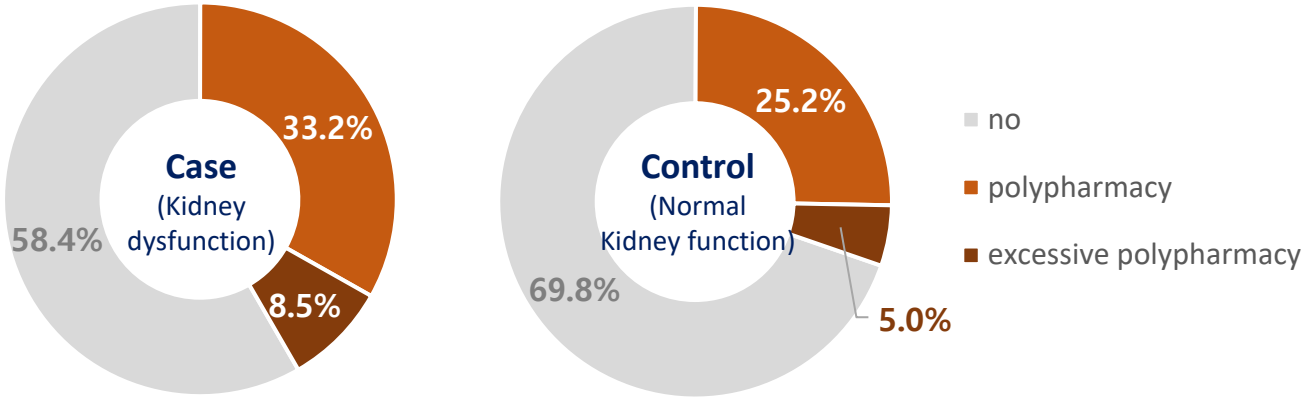
A retrospective case-control study (National Health Insurance Service- Senior Cohort)

14,557 patients who had developed kidney dysfunction (case) vs. control

Frequency of polypharmacy* according to kidney function**



Association between polypharmacy and kidney dysfunction

Variables	OR (95% CI)	Adjusted OR (95% CI)		
	Unadjusted	Model 1	Model 2	Model 3
Polypharmacy	1.572 (1.492-1.656)	1.287 (1.212-1.366)	1.301 (1.225-1.380)	**1.213** (1.139-1.292)
Excessive polypharmacy	2.069 (1.876-2.283)	1.603 (1.439-1.787)	1.589 (1.424-1.772)	**1.461** (1.303-1.639)

Model 1 was adjusted for lifestyle risk factors, Model 2 was adjusted for lifestyle risk factors and exposure to medication-related factors, Model 3 was adjusted for all risk factors

*Based on daily counts of pharmaceutical ingredients during one year prior to the case's event date, **Polypharmacy** : 5 to 10 ingredients **excessive polypharmacy** : 10 or more ingredients
****Kidney dysfunction** was defined as having an eGFR lower than 60, with a decline rate of 10% or more compared to the baseline eGFR.

Ref. Kang H and Hong S. Risk of Kidney Dysfunction from Polypharmacy among Older Patients: A Nested Case-Control Study of the South Korean Senior Cohort. Sci Rep 2019;9:10440.

Associative Risk Factors for Kidney Dysfunction among Korean older patients

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Associative risk factors for kidney dysfunction

Variables	OR (95% CI)	Adjusted OR (95% CI)		
	Unadjusted	Model 1	Model 2	Model 3
Hypertension	-	1.336 (1.265-1.412)	-	**1.141** (1.073-1.213)
Diabetes	-	1.122 (1.056-1.193)	-	**1.107** (1.021-1.200)
CHF	-	1.361 (1.186-1.562)	-	**1.329** (1.156-1.527)
Gout	-	1.912 (1.575-2.321)	-	**1.853** (1.507-2.277)
Hyper-TG (≥ 150 mg/dL)	-	1.171 (1.111-1.235)	-	**1.171** (1.111-1.235)
Lower-HDL-C (≤ 40mg/dL)	-	1.169 (1.090-1.254)	-	**1.171** (1.091-1.257)
Hyper-LDL-C (≥ 140 mg/dL)	-	1.000 (1.000-1.001)	-	**1.001** (1.000-1.001)

Model 1 was adjusted for lifestyle risk factors, Model 2 was adjusted for lifestyle risk factors and exposure to medication-related factors, Model 3 was adjusted for all risk factors

CHF, congestive heart failure; **TG**, triglyceride; **HDL-C**, high-density lipoprotein-cholesterol; **LDL-C**, low-density lipoprotein-cholesterol

Ref. Kang H and Hong S. Risk of Kidney Dysfunction from Polypharmacy among Older Patients: A Nested Case-Control Study of the South Korean Senior Cohort. Sci Rep 2019;9:10440.

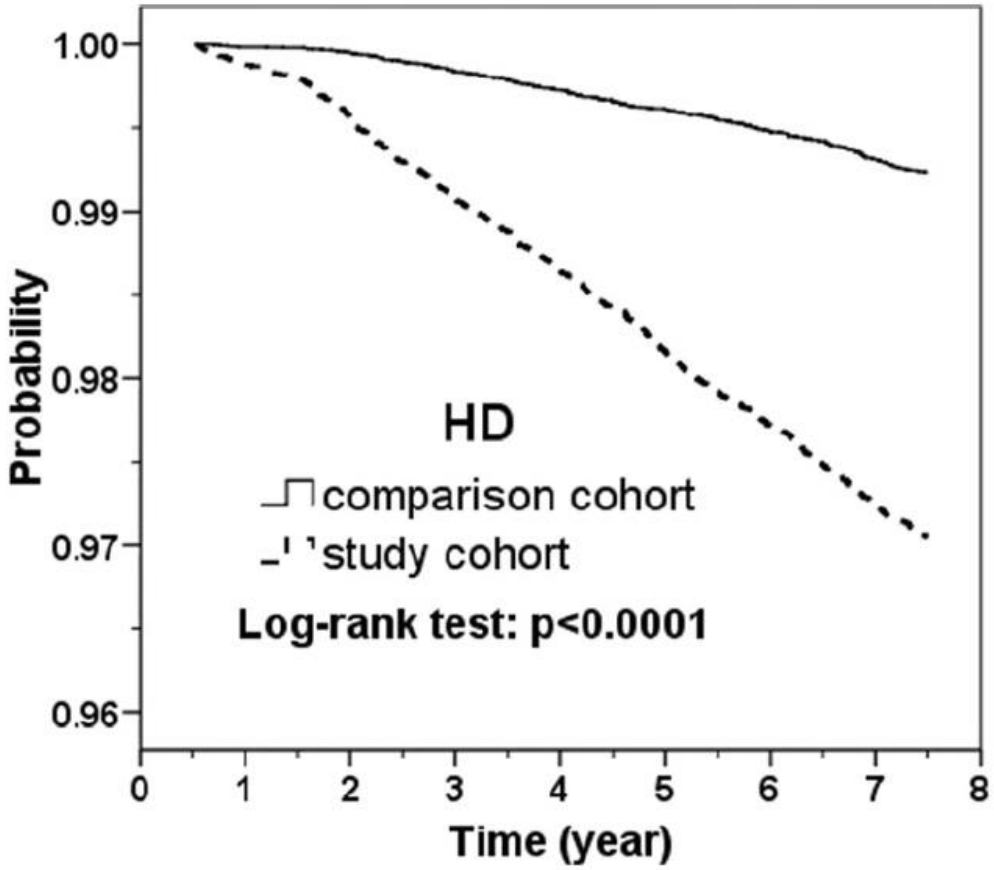
The risk for CKD in patients with heart diseases

A retrospective case control study (Taiwan)

26,005 patients with newly diagnosed heart disease vs. 52,010 people without such disease

Follow-up : 7 years

Kaplan-Meier plot for probability of subjects free from chronic kidney disease (CKD) in the follow-up period



Without heart disease
9.65/ 1000 person-year

X 4.1

With heart disease
39.51/ 1000 person-year

CKD, chronic kidney disease; **HD**, heart disease

Ref. Liu JH, et al. The risk for chronic kidney disease in patients with heart diseases: a 7-year follow-up in a cohort study in Taiwan. BMC Nephrol. 2012 Aug 3;13:77

Heart disease, DM and HTN are risk factors of CKD

Hazard ratios for risk factors of chronic kidney disease (CKD)

Variables	Model 1	Model 2	Model 3
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Heart disease			
No	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	4.10 (3.61-4.66)***	4.20 (3.70-4.78)***	2.37 (2.05-2.74)***
Sex			
Female		1.00 (reference)	1.00 (reference)
Male		1.50 (1.32-1.69)***	1.56 (1.38-1.77)***
Age			
< 40		1.00 (reference)	1.00 (reference)
40-49		3.79 (2.64-5.44)***	2.70 (1.87-3.88)***
50-59		5.32 (3.76-7.54)***	3.17 (2.22-4.52)***
≥ 60		9.23 (6.62-12.87)***	4.99 (3.55-7.03)***
DM			
No			1.00 (reference)
Yes			2.44 (2.13-2.80)***
Hypertension			
No			1.00 (reference)
Yes			2.26 (1.94-2.63)***
Hyperlipidemia			
No			1.00 (reference)
Yes			1.13 (0.99-1.30)

*p < 0.05, **p < 0.01,***p < 0.001.

Model 1: Cox hazard proportional analysis without adjustment. Model 2: Multivariate Cox hazard proportional analysis including age, sex, occupation, and income.

Model 3: Multivariate Cox hazard proportional analysis including age, sex, occupation, income, diabetes, hypertension, and hyperlipidemia. **CKD,** chronic kidney disease; **HD**, heart disease

Ref. Liu JH, et al. The risk for chronic kidney disease in patients with heart diseases: a 7-year follow-up in a cohort study in Taiwan. BMC Nephrol. 2012 Aug 3;13:77

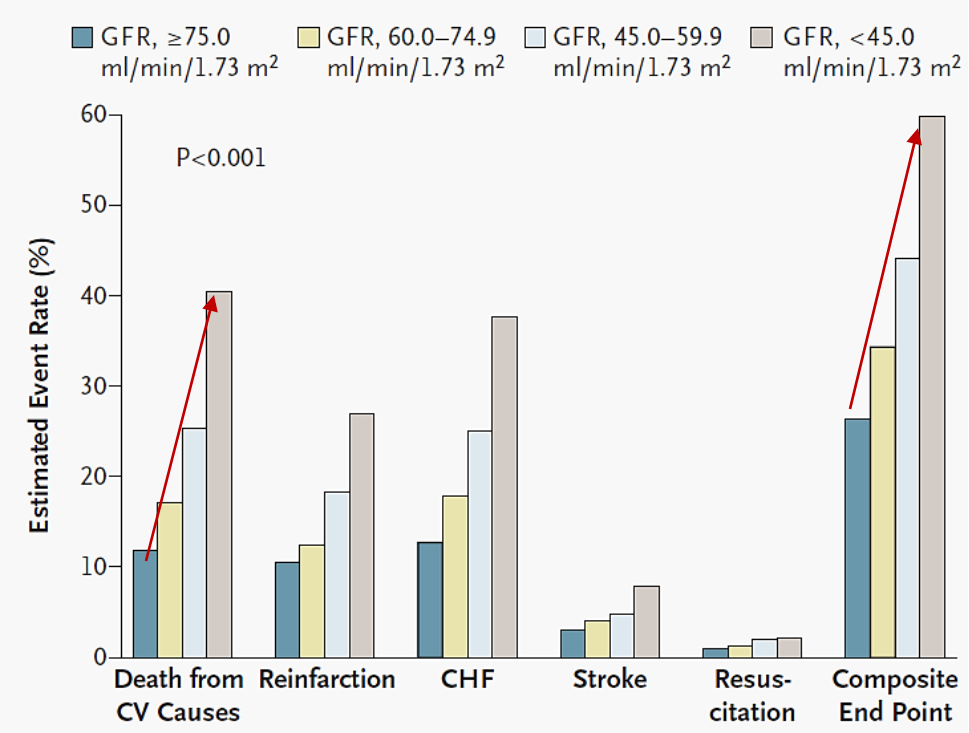
Relation between renal dysfunction and CV outcomes after MI

An analysis of double-blind, randomized, controlled trial, VALIANT study

14,527 patients with acute MI complicated by clinical or radiologic signs of HF, left ventricular dysfunction, or both and baseline serum creatinine level ≥ 2.5 mg/dL

Follow-up : median 24.7 months

Kaplan–Meier estimates of the rates of any cause death from and of the CV events according to the baseline eGFR (ml/min/1.73m²)



(ml/min/1.73m²)	GFR <45.0	GFR 45.0-59.9	GFR 60.0-74.9	GFR >75.0
(mg/dL)	Creatinine 1.7±0.4	Creatinine 1.3±0.2	Creatinine 1.1±0.1	Creatinine 0.9±0.1
Death (%)	**45.5**	**28.9**	**20.5**	**14.1**
Unadjusted HR (95% CI)	3.78 (3.39–4.21)	2.29 (2.07–2.53)	1.42 (1.28–1.58)	reference
Adjusted HR (95% CI)	**1.70** (1.50–1.93)	**1.38** (1.24–1.54)	**1.14** (1.02–1.27)	
Composite end point (%)	**59.9**	**44.1**	**34.3**	**26.5**
Unadjusted HR (95% CI)	2.94 (2.7–3.2)	1.92 (1.78–2.08)	1.33 (1.23–1.44)	reference
Adjusted HR (95% CI)	1.49 (1.35–1.65)	**1.26** (1.16–1.37)	**1.10** (1.02–1.19)	

*CV death, reinfarction, congestive heart failure, stroke, or resuscitation after cardiac arrest

VALIANT, The Valsartan in Acute Myocardial Infarction Trial; **MI**, myocardial infarction; **HF**, heart failure

Ref. Anavekar NS, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med. 2004 Sep 23;351(13):1285-95.

Relation between post-PCI AKI and CV outcomes after hospital discharge

An observational study from the NCDR CathPCI Registry (US 2004-2009)

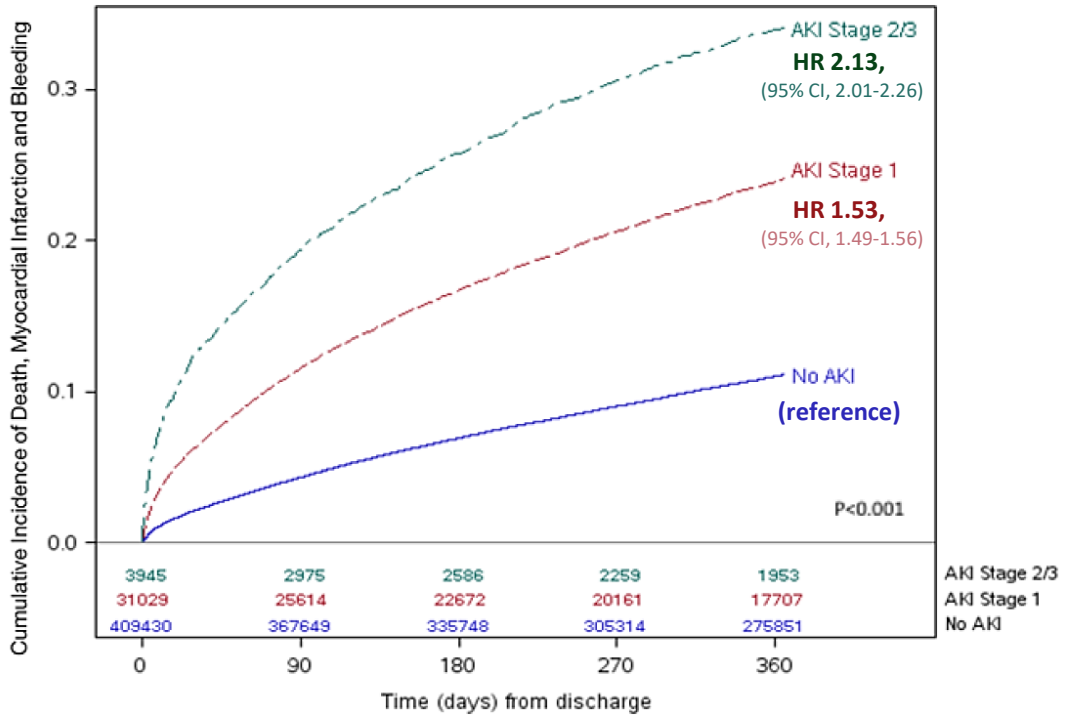
453,475 elderly patients undergoing PCI

Definition of AKI

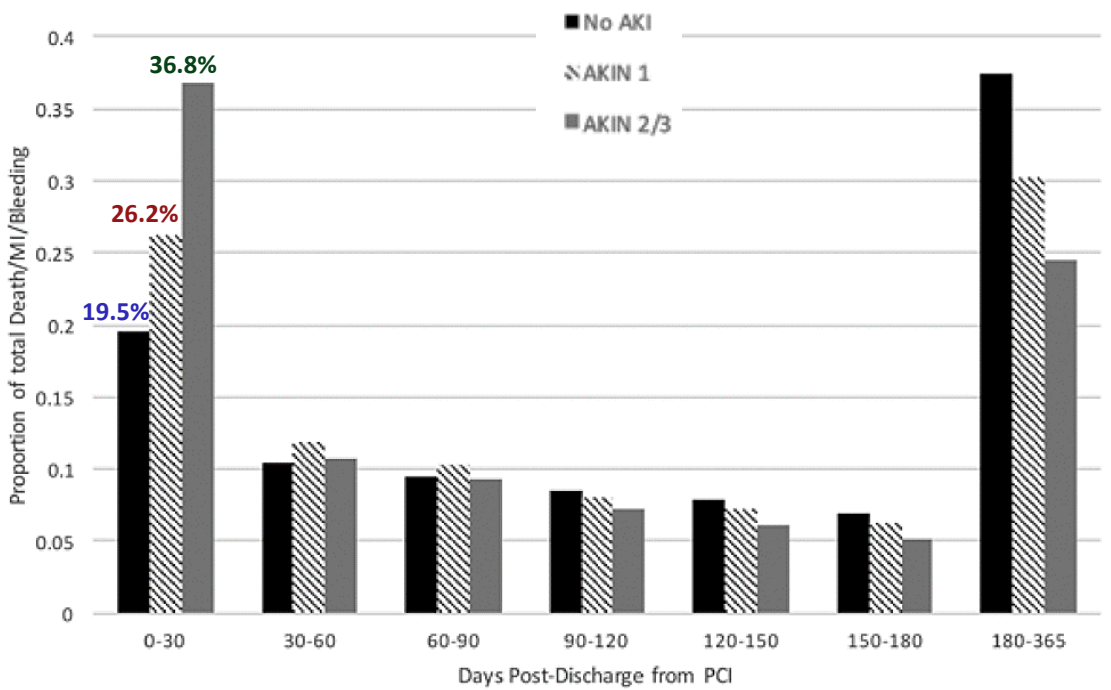
In-hospital AKI after PCI = **8.8%** (AKIN stage 1 : 85.8%)

AKIN stage 1 : Serum creatinine ≥ 0.3 mg/dL absolute or 1.5- to 2.0-fold increase from baseline
AKIN stage 2 : Serum creatinine 2.1- to 3.0-fold increase from baseline
AKIN stage 3 : Serum creatinine > 3.0-fold increase from baseline or dialysis

Cumulative incidence of adverse events* post-discharge



Timing of adverse events from hospital discharge



***Death, myocardial infarction, and bleeding**

PCI, percutaneous coronary intervention; **AKI**, Acute kidney injury; **NCDR**, National Cardiovascular Data Registry; **AKIN**, Acute Kidney Injury Network

Ref. Valle JA, et al. Longitudinal Risk of Adverse Events in Patients With Acute Kidney Injury After Percutaneous Coronary Intervention: Insights From the National Cardiovascular Data Registry. *Circ Cardiovasc Interv*. 2017;10(4):e004439.

Atorvastatin pretreatment and contrast-induced nephropathy in patients with ACS undergoing PCI

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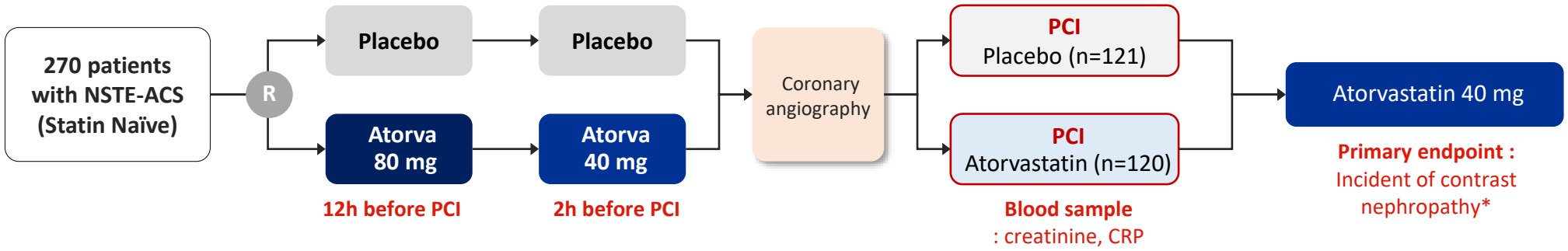
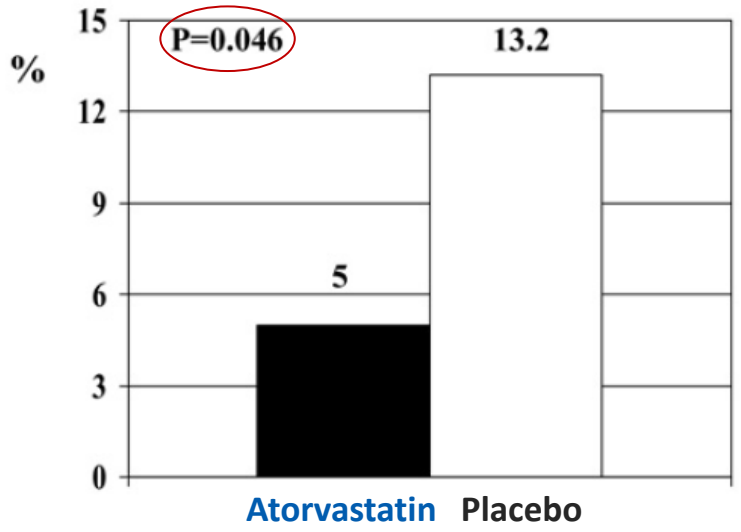
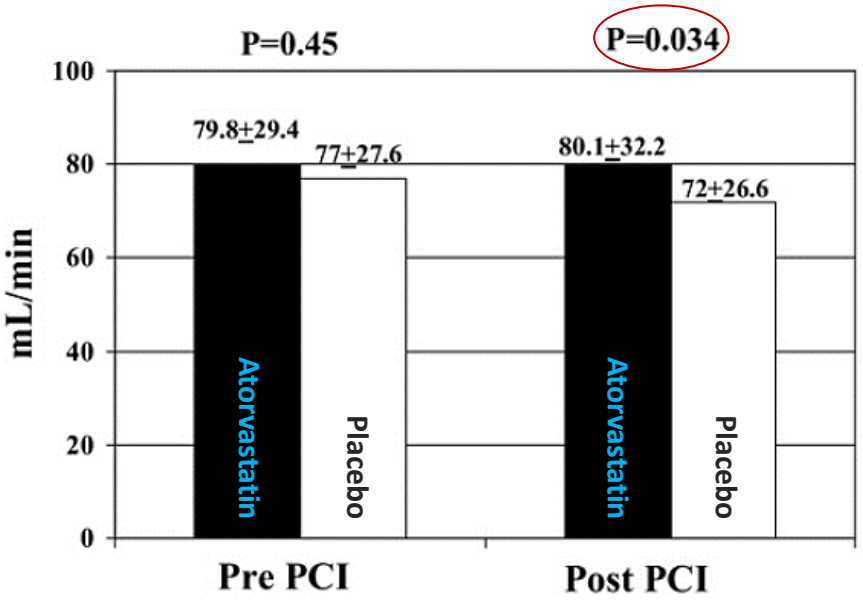
A randomized, multicenter, prospective, double-blind clinical trial (ARMYDA-CIN)



Incidence of contrast-induced nephropathy



Periprocedural creatinine clearance values



*serum creatinine >0.5 mg/dl or >25% from baseline

ARMYDA-CIN, atorvastatin for reduction of myocardial damage during angioplasty--contrast-induced nephropathy

Ref. Patti G, et al. Short-term, high-dose Atorvastatin pretreatment to prevent contrast-induced nephropathy in patients with acute coronary syndromes undergoing percutaneous coronary intervention (from the ARMYDA-CIN trial. *Am J Cardiol*. 2011;108(1):1-7.

Effect of atorvastatin on contrast-induced AKI in patients with CKD

LIPITOR® atorvastatin calcium trihydrate tablets
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A randomized, prospective, clinical trial (NAPLES II)

1,348 patients scheduled for elective coronary angiography or PCI (Statin naïve)

→ **eGFR < 60 ml/min/1.73m²**

→ R

- **Placebo (n=208)**
- Within 24 h before CM exposure
- Loading dose **Atorvastatin 80 mg (n=202)**

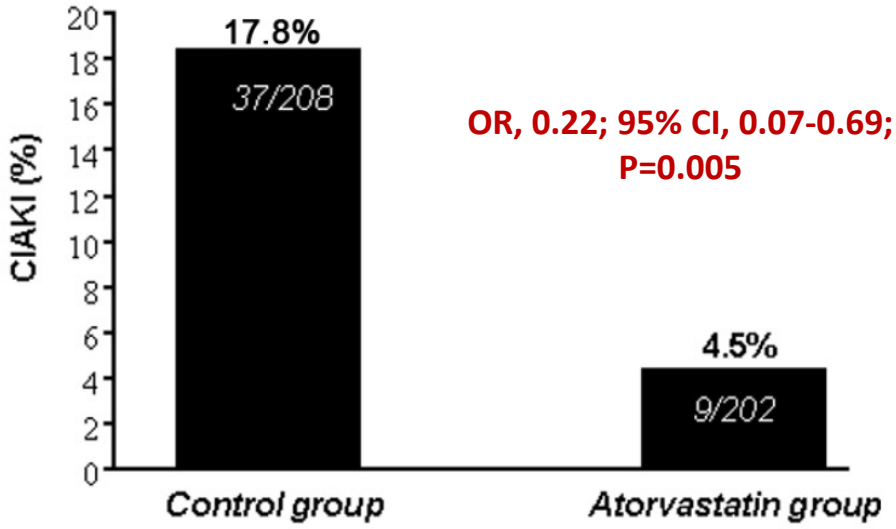
→ **Contrast media (CM) exposure**

→ **Atorvastatin 20 mg**

Primary endpoint : contrast-induced AKI*

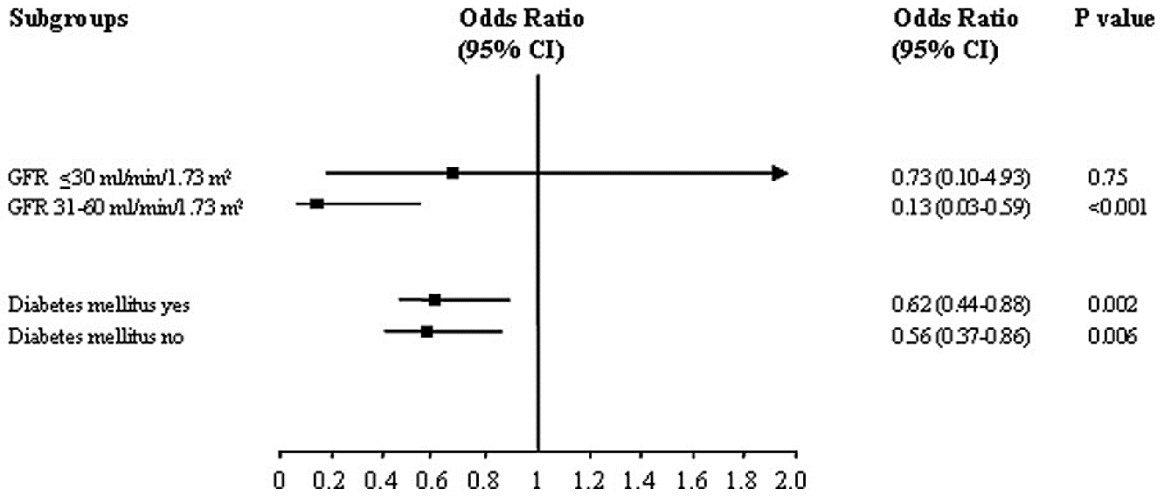
All patients received a high dose of N-acetylcysteine and sodium bicarbonate solution.

Incidence of contrast-induced AKI



OR, 0.22; 95% CI, 0.07-0.69; P=0.005

Benefit of atorvastatin according to severity of CKD and presence of DM



* Increase 10% of serum cystatin C

NAPLES, Novel Approaches for Preventing or Limiting Events; **CIAKI**, contrast induced acute kidney injury; **CKD**, chronic kidney disease; **CM**, contrast media; **DM**, diabetes mellitus

Ref. Quintavalle C, et al. Impact of a high loading dose of atorvastatin on contrast-induced acute kidney injury. *Circulation*. 2012;126(25):3008-3016.

Revascularization in Patients With Chronic Kidney Disease

COR	LOE	Recommendations
1 (strong)	C-LD (limited data)	**In patients with CKD** undergoing contrast media injection for coronary angiography, measures should be taken **to minimize the risk of contrast-induced acute kidney injury** (AKI).
1 (strong)	C-EO (expert opinion)	**In patients with STEMI and CKD,** coronary angiography and revascularization are recommended, with adequate **measures to reduce the risk of AKI.**
2a (moderate)	B-NR (non-randomized)	In high-risk patients with NSTE-ACS and CKD, it is reasonable to perform coronary angiography and revascularization, with adequate measures to reduce the risk of AKI.
2a (moderate)	C-EO (expert opinion)	In low-risk patients with NSTE-ACS and CKD, it is reasonable to weigh the risk of coronary angiography and revascularization against the potential benefit.
3: No benefit (harm strong)	B-R (randomized)	In asymptomatic patients with stable CAD and CKD, routine angiography and revascularization are not recommended if there is no compelling indication.

Best Practices in the Catheterization Laboratory For Patients With CKD Undergoing Angiography
• Assess the risk of contrast-induced AKI before the procedure
• Administer adequate preprocedural hydration
• Record the volume of contrast media administered, and minimize contrast use
• **Pretreat with high-intensity statins**
• Use radial artery if feasible
• Do not administer N-acetyl-L-cysteine to prevent contrast-induced AKI
• Do not give prophylactic renal replacement therapy
• Delay CABG in stable patients after angiography beyond 24 hours when clinically feasible

High-dose statins before diagnostic catheterization have been demonstrated to reduce the occurrence of contrast induced AKI because of their pleotropic effects that decrease systemic inflammation, possibly by decreasing the synthesis of ET-1 and inhibiting TF expression by macrophages.

ACC/AHA/SCAI, American College of Cardiology/ American Heart Association/ Society of Cardiovascular Angiography and Interventions; **CKD**, Chronic Kidney Disease; **COR**, class of recommendation; **LOE**, level of evidence; **STEMI**, ST-segment–elevation myocardial infarction; **NSTE-ACS**, non-ST-segment–elevation acute coronary syndrome; **CAD**, coronary artery disease; **CABG**, coronary artery bypass graft; ET-1, endothelin-1; **TF**, tissue-factor

Ref. Lawton JS, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice. *Circulation*. 2022;145(3):e4-e17.

2018 ESC/EACTS Guidelines on myocardial revascularization

Prevention of contrast induced nephropathy

Patients	Recommendations		Class[a]	Level[b]
Patients undergoing coronary angiography or MSCT	It is recommended that all patients are assessed for the risk of contrast induced nephropathy.		I	C
	Adequate hydration is recommended.		I	C
Patients with **moderate or severe CKD** (National Kidney Foundation stages 3b and 4)	Use of low-osmolar or iso-osmolar contrast media is recommended.		I	A
	It is recommended that the volume of contrast media be minimized.	Total contrast volume/GFR <3.7[c]	I	B
	In statin-naïve patients, pre-treatment with high dose statins should be considered.	**Atorvastatin 80 mg or Rosuvastatin 40/20 mg**	IIa	A
	Pre- and post-hydration with isotonic saline should be considered if the expected contrast volume is >100 mL.	1 mL/kg/h 12 h before and continued for 24 h after the procedure (0.5 mL/ kg/h if LVEF ≤ 35% or NYHA >2)	IIa	C
	As an alternative to the pre- and post- hydration regimen, tailored hydration regimens[d] may be considered.		IIb	B
Patients with **severe CKD** (National Kidney Foundation stage 4)	Prophylactic haemofiltration 6 h before complex PCI may be considered	Fluid replacement rate 1000 mL/h without negative loss and saline hydration continued for 24 h after the procedure.	IIb	B
	Haemodialysis is not recommended as a preventive measure.		III	B

High-dose statins, as indicated for secondary prevention irrespective of the risk of CIN are also beneficial.

[a]Class of recommendation; [b]Level of evidence; [c]Example: 370 mL of contrast medium in a patient with a GFR of 100 mL/min will yield a ratio of 3.7; [d]Options are: infusion of normal saline adjusted to central venous pressure295 or furosemide with matched infusion of normal saline
ESC/EACTS, European Society of Cardiology and European Association for Cardio-Thoracic Surgery; **MSCT**, multi-slice computed tomography; **NYHA**, New York Heart Association; **LVEF**, left ventricular ejection fraction

Ref. Neumann FJ, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization [published correction appears in Eur Heart J. 2019 Oct 1;40(37):3096]. *Eur Heart J.* 2019;40(2):87-165.

Renal Safety of Atorvastatin

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The statin with the lowest renal excretion rate
Atorvastatin

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Lipid-lowering efficacy and pharmacologic characteristics of statins

		Lovastatin	Pravastatin	Simvastatin	Atorvastatin	Fluvastatin	Rosuvastatin	Pitavastatin
Daily dose (mg)		20-40	10-40[a]	20-40	10-80	20-80	5-20[b]	1-4
LDL-C Reduction (%)	24-28%	20	20			40		1
	30-36%	40	40	20	10	80		2
	39-45%	80		40	20		5-10	4
	46-52%				40-80		20	
Metabolism		CYP3A4	Sulfonation	CYP3A4	CYP3A4	CYP2C9	CYP2C9	Glucuronidation (Partial CYP2C9)
Protein binding (%)		>95	43-67	95-98	98	98	88	>99
Half-life (h)		2-4	2-3	1-3	13-30	0.5-3	19	12
Hydrophilicity		–	+	–	–	–	+	–
Elimination		Hepatobiliary	Hepatobiliary	Hepatobiliary	Hepatobiliary	Hepatobiliary	Hepatobiliary	Hepatobiliary
Renal elimination Fraction (%)		**10**	**20**	**13**	**<2**	**<6**	**28**	**15**

[a]40~80 mg in Caucasian countries. [b]5~40 mg in Caucasian countries

Ref. 한국지질·동맥경화학회, 2022 이상지질혈증 진료지침 제5판

Effect of moderate-intensity atorvastatin on renal function in patients with diabetic patients

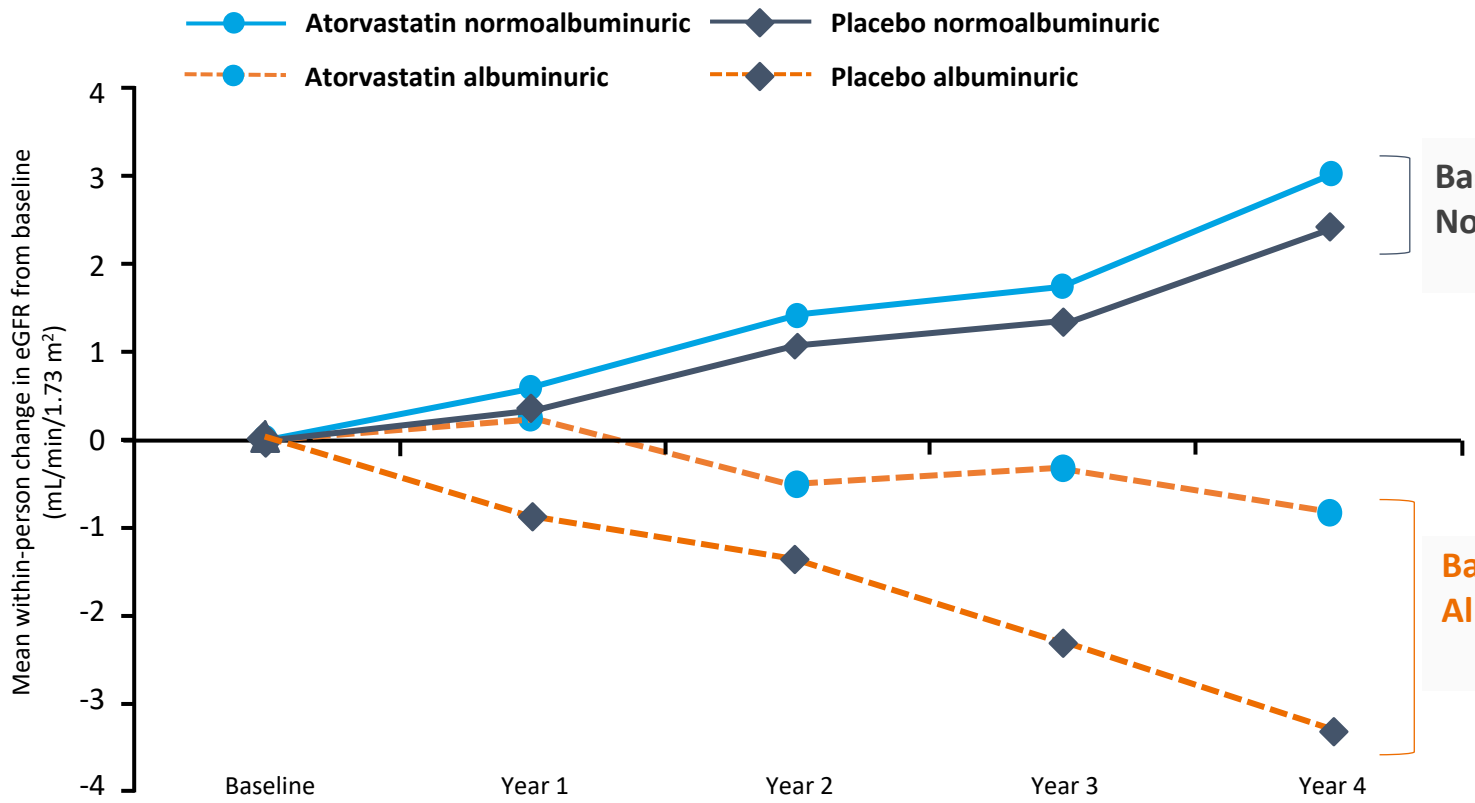
LIPITOR® atorvastatin calcium trihydrate tablets

LIPITOR® Plus Tab. (Ezetimibe/Atorvastatin calcium trihydrate)

An analysis from the Collaborative Atorvastatin Diabetes Study (CARDS)

2,838 patients with type 2 diabetes and no prior cardiovascular disease

[CARDS] Yearly mean within-person change in eGFR by treatment group and baseline albuminuria



	Net effect of atorvastatin on eGFR
Baseline Normoalbuminuria :	+0.13 mL/min/1.73 m²/year (p=0.1)
Baseline Albuminuria :	+0.38 mL/min/1.73 m²/year (p=0.03)

CARDS, The Collaborative Atorvastatin Diabetes Study; **eGFR**, estimated glomerular filtration rate; **ACR**, albumin-creatinine ratio

Ref. Colhoun HM et al. Effects of atorvastatin on kidney outcomes and cardiovascular disease in patients with diabetes: an analysis from the Collaborative Atorvastatin Diabetes Study (CARDS). Am J Kidney Dis 2009;54:810-819.

Effect of moderate-intensity atorvastatin on eGFR changes in Korean diabetic patients

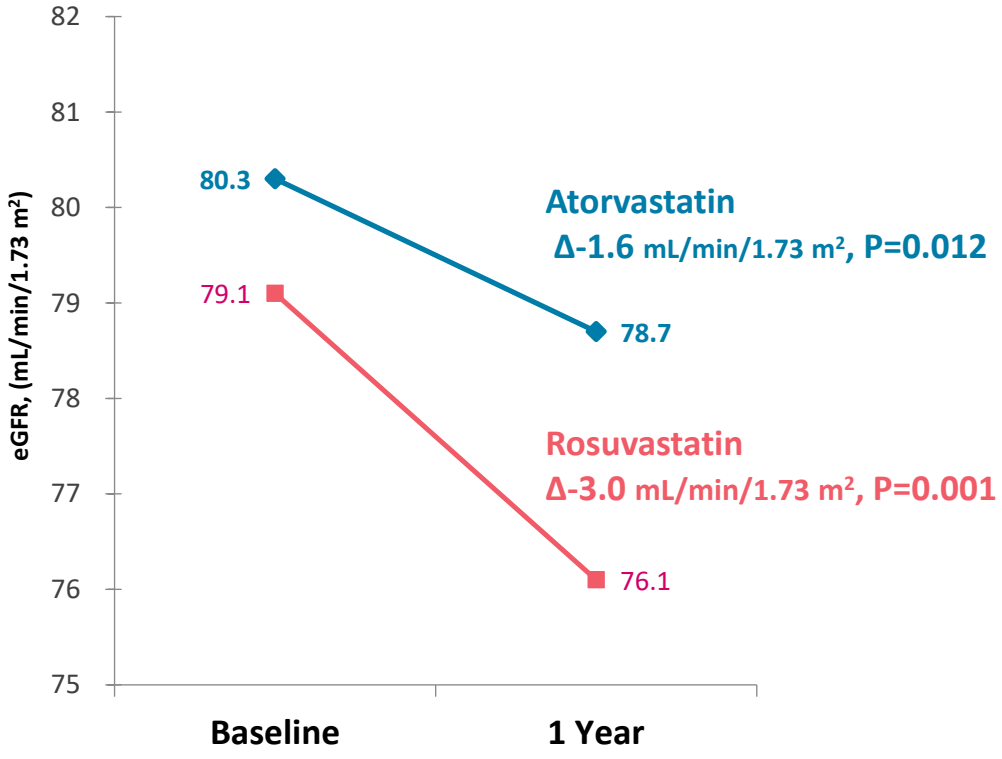
LIPITOR® atorvastatin calcium trihydrate tablets
LIPITOR® Plus Tab. (Ezetimibe/Atorvastatin calcium trihydrate)

A retrospective analysis study

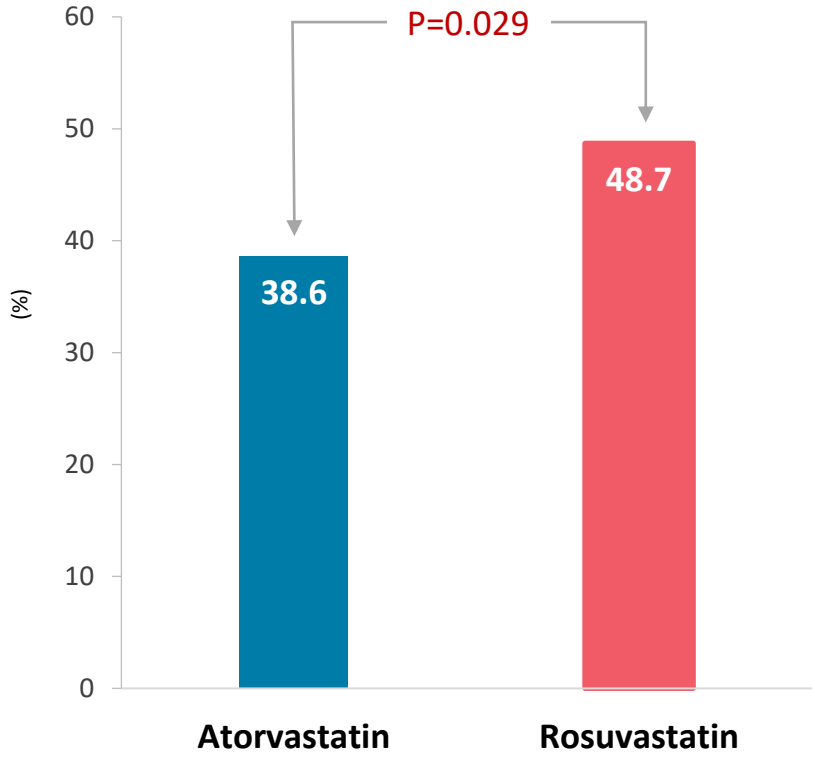
484 patients with diabetes who received statin treatment for more than 12 months

Moderate-intensity dose statin : atorvastatin 10-20 mg/day or rosuvastatin 5-10 mg/day

Changes in eGFR after statin use 1 year



% with patient experienced rapid renal function decline*



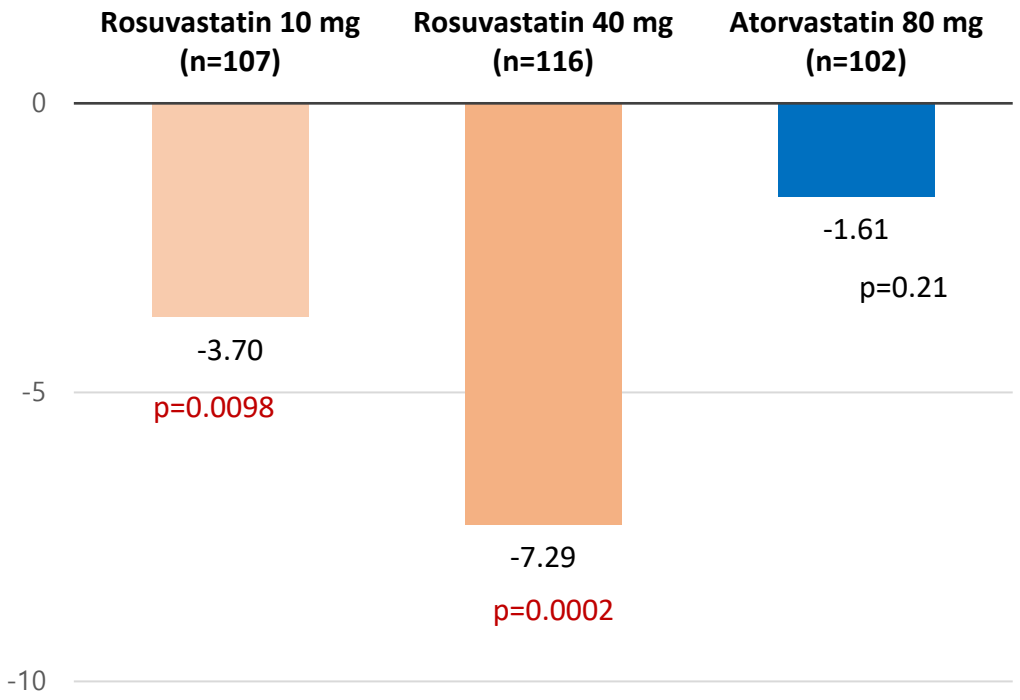
*>3% reduction in eGFR in a 1-year period

Ref. Han E, et al. Comparison between Atorvastatin and Rosuvastatin in Renal Function Decline among Patients with Diabetes. Endocrinol Metab 2017;32:274-280.

Renal effects of high-intensity atorvastatin in patients with diabetes who have progressive renal disease

A randomized double-blind, parallel-group trial (PLANET I)
325 patients with diabetes who have progressive renal disease

Change in eGFR (mL/min/1.73 m^2, baseline vs week 52)



Adverse events in the safety population (n, %)

	Rosuvastatin 10 mg (n=116)	Rosuvastatin 40 mg (n=123)	Atorvastatin 80 mg (n=110)
Any adverse event	69 (59.5)	79 (64.2)	63 (57.3)
Any serious adverse event	18 (15.5)	20 (16.3)	21 (19.1)
Any renal adverse event	9 (7.8)	12 (9.8)	5 (4.5)
Creatinine doubling	0	6 (4.9)	0
Acute renal failure	0	5 (4.1)	1 (0.9)
Doubling of serum creatinine or acute renal failure	0	9 (7.3)	1 (0.9)
Death	4 (3.4)	1 (0.8)	0

PLANET, Prospective Evaluation of Proteinuria and Renal Function in Diabetic Patients with Progressive Renal Disease; **eGFR**, estimated glomerular filtration rate

Ref. De Zeeuw D, et al. Renal effects of atorvastatin and rosuvastatin in patients with diabetes who have progressive renal disease (PLANET I): a randomised clinical trial. Lancet Diabetes Endocrinol 2015;3:181-90.

A multicenter observational cohort study in US

Association of atorvastatin use with risk of proteinuria

EHR data from 40 health care organizations (“cohorts”) participating in Optum Labs Data Warehouse to conduct a multicenter observational cohort study.

Patients aged ≥18 years between 2011 and 2019
(Had ≥1 year of prior engagement with the health system, were free of kidney failure with replacement therapy (KFRT), did not have history of any study outcome (i.e.,hematuria, proteinuria), did not have any statin prescriptions within the year before study medication initiation (baseline, T0))

Rosuvastatin new users (n=152,101)

Atorvastatin new users (n=795,799)

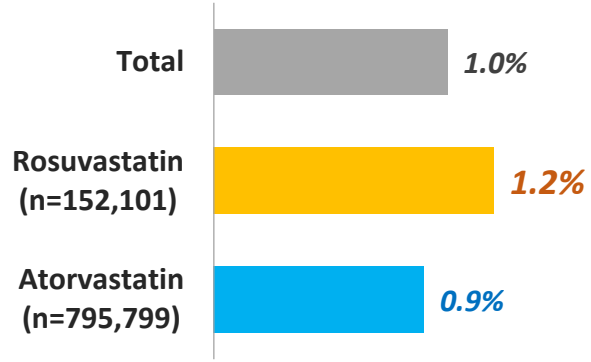
Outcome

- **Hematuria :** dipstick hematuria ≥ + or presence of ≥ 3 red blood cells in urine microscopy
- **Proteinuria :** dipstick proteinuria ≥ ++ or urine albumin-creatinine ratio ≥ 300 mg/g
- **Kidney failure with replacement therapy (KFRT)**

Ref. Shin JI, et al. Association of Rosuvastatin Use with Risk of Hematuria and Proteinuria. J Am Soc Nephrol. 2022 Sep;33(9):1767-1777.

Low incidence rate of proteinuria in atorvastatin

Incidence of proteinuria in Rosuvastatin use, Atorvastatin use and overall



IPTW analysis : Incidence rate of proteinuria per 1000 person-year, overall and across eGFR levels

		IPTW-IR (95% CI), per 1000 PYs		IPTW-HR (95% CI)	P for Heterogeneity[a]
		Rosuvastatin	Atorvastatin		
	Overall	3.2 (3.1 to 3.4)	2.8 (2.7 to 2.8)	**1.17 (1.10 to 1.25)**	
eGFR (mL/min per 1.73 m^2)	≥ 60	2.4 (2.3 to 2.6)	2.1 (2.0 to 2.2)	1.16 (1.07 to 1.25)	**0.74**
	30-59	7.8 (7.1 to 8.6)	6.7 (6.4 to 7.0)	1.18 (1.06 to 1.31)	
	<30	22.6 (17.1 to 30.6)	20.5 (18.3 to 23.1)	1.10 (0.81 to 1.50)	

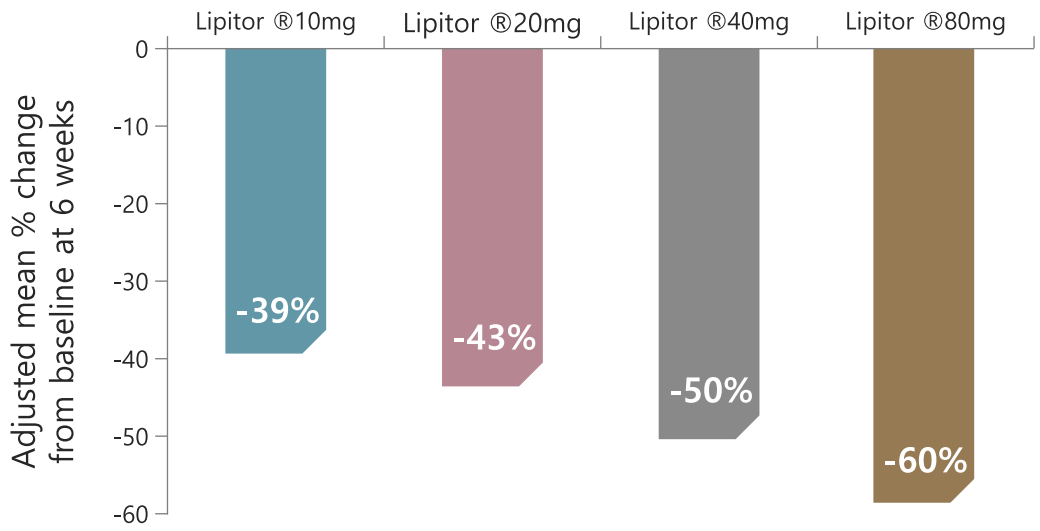
[a]P for heterogeneity in HR was estimated using stratified Cox models with interaction term between rosuvastatin use and eGFR category.

IPTW, inverse probability of treatment weighting; **IR**, incidence rate; **PYs**, person-years

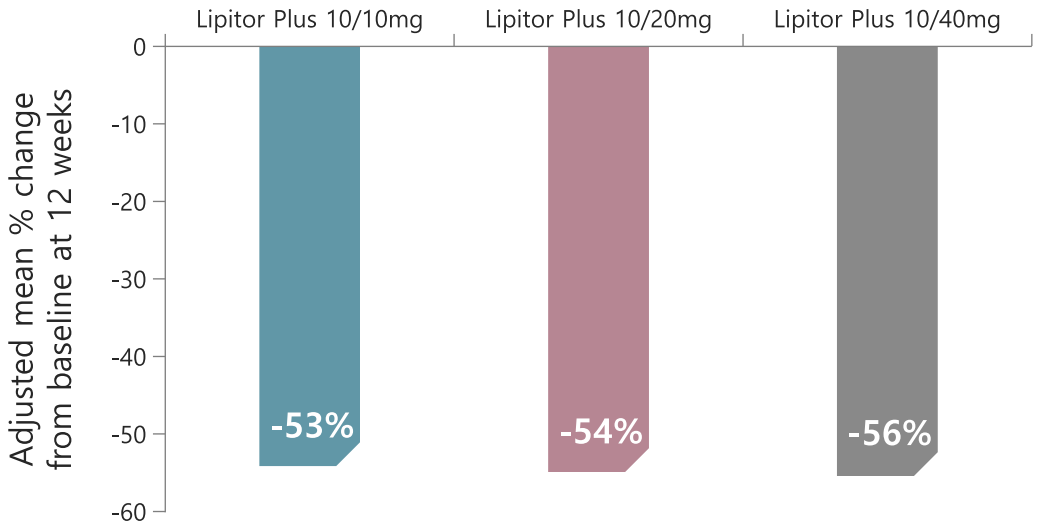
Ref. Shin JI, et al. Association of Rosuvastatin Use with Risk of Hematuria and Proteinuria. J Am Soc Nephrol. 2022 Sep;33(9):1767-1777.

Lipitor Portfolio (Lipitor & Lipitor Plus)

LDL-C reduction of Lipitor [3,*]



LDL-C reduction of Lipitor Plus [5,*]



- **7 dose options**
- **Lipitor Plus uses the same Atorvastatin API as Lipitor**
- **Lipitor Plus was developed to be up to 17% smaller in size than the original design formulation for convenience.**

*Adjusted mean % change from baseline. Results are pooled from 2 multicenter, placebo-controlled, dose-response studies in patients with primary hyperlipidemia.
LIPITOR was given as a single dose over 6 weeks. †Results are from a multicenter, double-blind, placebo-controlled, clinical study in patients with primary hyperlipidemia

ESC, European Society of Cardiology; KSoLA, Korean Society of Lipid and Atherosclerosis; LDL-C, low-density lipoprotein cholesterol

Ref. 1. 한국지질동맥경화학회. 이상지질혈증 진료지침 제5판. 2022. 2. Visseren FLJ, Mach F, Smulders YM, *et al.* 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021 Sep 7;42(34):3227-3337. 3. LIPITOR® (atorvastatin calcium). US PI. Revised:12/2022. 4. 식품의약품안전처 의약품통합정보시스템. 의약품등 제품정보 검색. 리피토정. Available at <https://nedrug.mfds.go.kr/searchDrug> accessed on Jan 31, 2024. 5. LIPTRUZET® (ezetimibe and atorvastatin). US PI. Revised:9/2020. 6. 식품의약품안전처 의약품통합정보시스템. 의약품등 제품정보 검색. 리피토플러스정. Available at <https://nedrug.mfds.go.kr/searchDrug> accessed on Jan 31, 2024.

Summary

- Even in the absence of kidney disease, kidney function declines with age, it is important to consider the effect on the kidneys when considering statins.
- Heart disease significantly increases the risk of developing chronic kidney disease, and conversely, the lower the eGFR, the higher the risk of death and CV events in MI patients.
- Undergoing PCI, contrast-induced nephropathy may occur, and pretreatment with high-intensity atorvastatin had a significantly lower incidence of renal damage compared to placebo.
- Therefore, when considering the statin, it is important to select a statin that does not affect the kidneys. Atorvastatin has the lowest renal excretion rate among statins.
- In addition, Atorvastatin did not show a decrease in eGFR in both diabetes and CHD patient groups, and it showed that the low incidence of proteinuria in a multicenter observational cohort study (US).

리피토® 정 제품요약 정보

LIPITOR® atorvastatin calcium trihydrate tablets

리피토® 정 10 mg, 20 mg, 40 mg, 80 mg 제품설명서 요약정보

[Safety info.] 당뇨병이 발생할 위험성이 높은 몇몇 환자들에게서 적절한 당뇨병 치료를 요하는 과혈당증을 유발할 수 있다는 몇 가지 증거가 제시됨. 그러나 스타틴 제제의 혈관성 위험성 감소효과는 이러한 위험성을 상회하므로 스타틴 치료중단의 사유가 될 수 없음. 위험성이 있는 환자 (공복혈당 5.6~6.9 mmol/L, BMI>30kg/m^2, 중성지방수치 상승, 고혈압)들은 진료지침에 따라 임상적 및 실험실적 수치 모니터링을 실시해야 함.

[제품명·성분명] 리피토 정 Lipitor Tab. (Atorvastatin Calcium 10 mg, 20 mg, 40 mg, 80 mg) **[성상]** 흰색의 원형 필름코팅정제 **[성분·함량]** 매 정당 아토르바스타틴 칼슘 삼수화물 10.85 mg, 21.70 mg, 43.40 mg, 86.80 mg (아토르바스타틴으로서 각각 10 mg, 20 mg, 40 mg, 80 mg) **[효능·효과]** 관상동맥 심장질환 다중위험 요소를 가진 성인의 심근경색증/뇌졸중/혈관 재생술/만성 안정형 협심증에 대한 위험성 감소, 관상동맥 심질환 다중위험요소를 가진 제2형 당뇨병 환자의 심근경색증/뇌졸중에 대한 위험성 감소, 관상동맥 심장질환에 대한 임상적 증거가 있는 성인 환자의 비치명적 심근경색증/치명적 및 비치명적 뇌졸중/혈관재생술/울혈성 심부전으로 인한 입원/협심증에 대한 위험성 감소, 고지혈증 환자의 식이요법 보조제, 이형 접합 가족형 고콜레스테롤혈증의 10~17세 소아(여아의 경우 초경 이후)의 식이요법 보조제 **[용법·용량]** 1일 1회 10 mg, 20 mg, 40 mg으로 시작, 최고용량 80 mg까지 음식물과 상관없이 하루 중 아무 때나 투여 가능 **[사용상의 주의 사항] [경고]** 현저한 크레아틴 키나아제(CK) 레벨 상승이 나타나거나 근육병증으로 진단되거나 의심되는 경우 아토르바스타틴 치료를 중단해야 한다. 또한 급성 및 심각하게 여겨지는 근육병증 또는 횡문근융해에서 이차적으로 신부전으로 발전할 수 있는 위험요소(예, 중증 급성감염, 저혈압, 주요 외과수술, 외상, 중증 대사, 내분비, 전해질 장애 및 제어되지 않는 간질)를 갖는 환자는 아토르바스타틴 치료를 일시적으로 보류 또는 중단해야 한다. **[금기]** 이 약의 구성 성분에 과민한 환자, 활동성 간질환 환자 또는 혈청 트랜스아미나제치의 상승이 정상상한치의 3배 이상 상승된 환자, 근질환 환자, 임부, 수유부, 피임제를 사용하지 않는 가임여성, 10세 미만의 소아, 글레카프레비르 및 피브렌타스비르를 투여중인 환자, 갈락토오스 불내성, Lapp 유당분해효소 결핍 증, 또는 포도당-갈락토오스 흡수장애 등의 유전적인 문제가 있는 환자, 급성 간 부전 또는 비대상성 간경화 환자 **[신중투여]** 알코올 중독자 또는 간질환의 병력이 있는 환자, 횡문근융해에 대한 소인이 있는 **[이상반응]** 여러 임상 결과에서 나타난 가장 흔한 이상반응은 때때로 무력감, 권태감, 가슴통증, 말초부종, 피로, 발열, 근육통 등이었음. 일부 스타틴과 관련하여 수면장애, 기억상실, 우울, 장기투여 시 간질성 폐질환과 같은 예외적 사례, 성적 기능이상이 보고됨. **[일반적 주의]** 향후 당뇨병이 발생할 위험성이 높은 몇몇 환자들에게서 적절한 당뇨병 치료를 요하는 과혈당증 을 유발 할 수 있다는 몇 가지 증거가 제시되었다. 그러나 스타틴 제제의 혈관성 위험성 감소효과는 이러한 위험성을 상회하므로 스타틴 치료 중단의 사유가 될 수 없다. 위험성이 있는 환자(공복혈당 5.6~6.9mmol/L, BMI>30kg/m^2, 중성지방수치 상승, 고혈압)들은 진료 지 침에 따라 임상적 및 실험실적 수치 모니터링을 실시해야 한다. **[상호작용]** 시클로스포린과 병용투여 시 아토르바스타틴의 투여용량은 10 mg을 초과해서는 안됨 [**제품설명서 개정년월일]** 2024.03.12

※ 제품에 대한 자세한 내용은 최신의 제품설명서를 참고하시기 바라며, 홈페이지(www.viatris.co.kr)에서 확인할 수 있습니다.

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