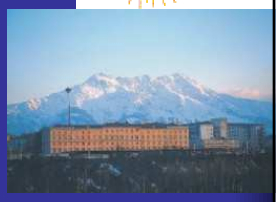
A.S.O. "S.Croce e Carle"
Cuneo
S.C. Endocrinologia, Diabetologia e Metabolismo
S.S. Malattie Metaboliche e Diabetologia
S.C. Nefrologia



La cura del Diabete in Ospedale: il paziente con insufficienza renale

Altre terapie di comune impiego nel paziente diabetico: Ipolipemizzanti, anticonvulsivanti, inibitori della fosfodiesterasi

Relatore: G. Magro (Cuneo)

Sabato, 25 Gennaio 2014

La nefropatia diabetica si manifesta nel 20-40% dei pazienti diabetici

Tutti gli individui con nefropatia diabetica devono essere considerati a elevato rischio di eventi cardiovascolari e dovrebbero essere trattati per ridurre tale rischio, attraverso un intervento mirato a correggere tutti i fattori di rischio. **(Livello della prova I, Forza della raccomandazione A)**

Ottimizzare il controllo degli altri fattori di rischio (lipidi, fumo) per rallentare la progressione della nefropatia (Livello della prova I, Forza della raccomandazione B)

Standard italiani per la cura del diabete mellito 2009-20210; SID

BMJ

Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomised controlled trials

Giovanni F M Strippoli, editor of Cochrane Renal Group,[1,2,3] Sankar D Navaneethan, clinical fellow in nephrology,[4] David W Johnson, professor of nephrology,[5] Vlado Perkovic, associate director (clinical research),[6] Fabio Pellegrini, biostatistician,[2] Antonio Nicolucci, head,[2] Jonathan C Craig, editor in chief of Cochrane Renal Group and associate professor of epidemiology[1,3]

Table 2 | Effects of statins on lipid concentrations and renal function in patients with chronic kidney disease

Outcome	No of trials (No of patients)	Weighted mean difference (95% CI)	Heterogeneity (I^2; %)
Total cholesterol (mg/dl)*	42 (6390)	−42.28 (−47.25 to −37.32)	94.9
LDL cholesterol (mg/dl)*	39 (6216)	−43.12 (−47.85 to −38.40)	94.1
HDL cholesterol (mg/dl)*	40 (5621)	0.41 (−0.78 to 1.60)	94.4
Triglycerides (mg/dl)†	39 (5569)	−23.71 (−33.52 to −13.90)	89.5
Glomerular filtration rate (ml/min or ml/min/1.73 m^2)	11 (548)	1.48 (−2.32 to 5.28)	62.0
Urinary protein excretion (g/24 h)	6 (311)	−0.73 (−0.95 to −0.52)	58.6

HDL=high density lipoprotein; LDL=low density lipoprotein.
*Multiply by 0.0259 to convert to mmol/l.
†Multiply by 0.01 to convert to mmol/l.

Conclusions:
These results suggest that statin treatment is safe and reduces the risk of major cardiovascular events in patients with chronic kidney disease in a similar fashion to that seen in trials of statins in non-chronic kidney disease populations.
These agents may have antiproteinuric effects, although the clinical significance of these benefits remains uncertain. We did not show an effect on all cause mortality, but this may reflect inadequate statistical power.

Accepted: 11 January 2008

BMJ

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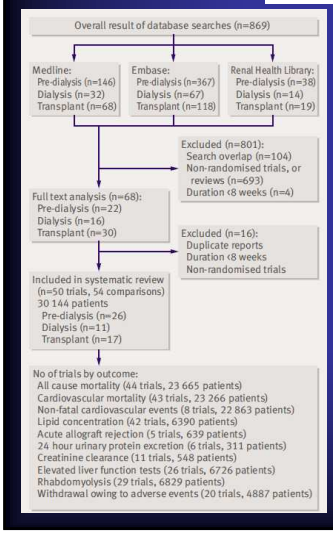

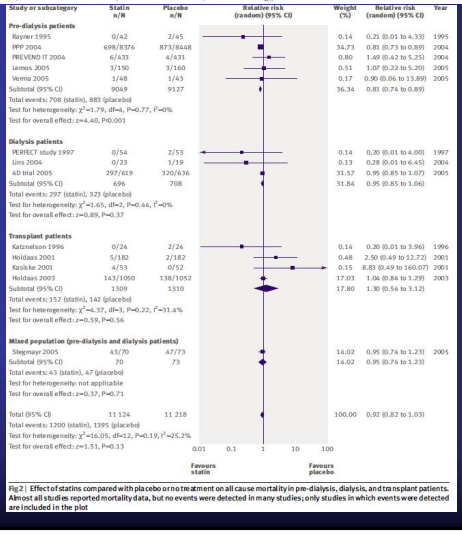

Fig 2 | Effect of statins compared with placebo or no treatment on all cause mortality in pre-dialysis, dialysis, and transplant patients. Almost all studies reported mortality data, but no events were detected in many studies; only studies in which events were detected are included in the plot

BMJ

Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomised controlled trials

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WHAT IS ALREADY KNOWN ON THIS TOPIC

Patients with chronic kidney disease are at increased risk of cardiovascular disease

Statins reduce cardiovascular mortality and all cause mortality in the general population

The role of statins in chronic kidney disease is controversial

WHAT THIS STUDY ADDS

Statins reduce cardiovascular deaths in patients with chronic kidney disease by a similar rate to that seen in the general population

The efficacy of statins in reducing all cause mortality in kidney disease patients and their role in primary prevention need to be established in ongoing trials

Statins are safe as regards major side effects such as hepatotoxicity, rhabdomyolysis, and treatment withdrawal

Accepted: 11 January 2008

BMJ

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Le statine riducono in maniera significativa le concentrazioni lipidiche e gli end point cardiovascolari in pazienti con malattia renale cronica, indipendentemente dallo stadio della malattia. Non sono stati osservati benefici significativi del trattamento con statine sulla mortalità per tutte le cause. Gli effetti protettivi renali delle statine sono incerti.

Dalla metanalisi emerge che il trattamento con statine in pazienti in pre-dialisi riduce il rischio di mortalità per tutte le cause del 19%, valore che è assimilabile al beneficio legato allo stesso trattamento nella popolazione generale. Quando l'analisi viene estesa ai pazienti dializzati e a quelli trapiantati il beneficio scompare. Viene confermato invece un rischio inferiore di mortalità legata a cause cardiovascolari. In termini di tollerabilità, non sono state rilevate differenze relativamente al rischio di alterazioni epatiche o muscolari (aumento CPK). Questi risultati suggeriscono che il beneficio osservato per le statine nella popolazione generale si applica anche ai pazienti con velocità di filtrazione glomerulare ridotta e a quelli dializzati.

La metanalisi dimostra che le statine possono ridurre la proteinuria in modo modesto ma non influenzano i tempi di declino della velocità di filtrazione glomerulare. Inoltre non ci sono studi che abbiano valutato come esito la progressione della malattia fino allo stadio finale.

Non ci sono prove di effetti benefici delle statine che vadano oltre alla riduzione del rischio cardiovascolare mentre sono possibili effetti avversi che devono spingere a una prescrizione appropriata.

Accepted: 11 January 2008

STANDARD ITALIANI PER LA CURA DEL DIABETE MELLITO 2009-2010

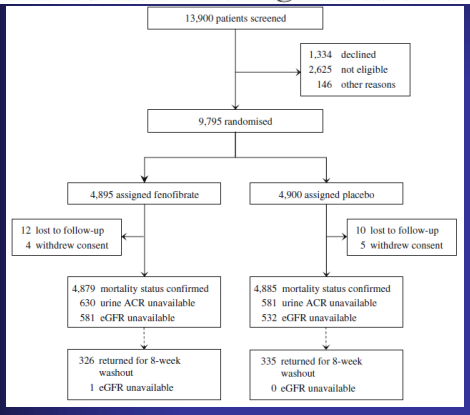
Trattamento dislipidemia nella nefropatia Diabetica:

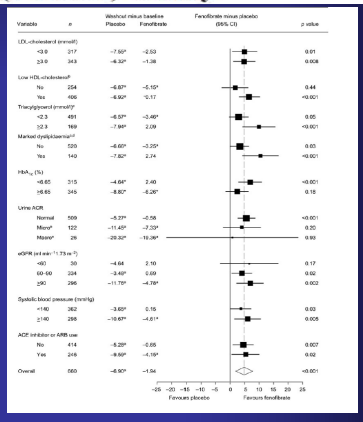
Non sono disponibili studi randomizzati, che abbiano documentato effetti protettivi delle statine sulla progressione della nefropatia diabetica.

Lo studio FIELD ha documentato una riduzione dell'albuminuria e un rallentamento della curva di perdita del filtrato glomerulare associata all'uso del fibrato.

L'associazione statina-ezetimibe ha dimostrato un effetto benefico sulla progressione delle nefropatie croniche (Studio SHARP).

Effects of fenofibrate on renal function in patients with type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study





In conclusion, we demonstrated in pre-specified analyses that fenofibrate reduces albuminuria progression and may reduce loss of renal function. This appears to be independent of, and therefore additive to renin–angiotensin system blockade and glycaemic control. The size and consistency of the estimated GFR and albuminuria benefits support use of fenofibrate in type 2 diabetes to reduce renal morbidity, especially in patients with dyslipidaemia

Diabetologia (2011) 54:280–290

Benefits of Lipid lowering in Stages of CKD

CKD stage	CV events ↓	Based on trial
1	Yes	Post-hoc analysis from: Care, HPS, TNT, 4S, AFCAPS/ Texcaps, VA-HIT
2	Yes	
3	Yes	
4	Yes	SHARP
5	Yes	SHARP
Dialysis	Probably	SHARP (4D, Aurora)
Transplant	Probably	ALERT

The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial

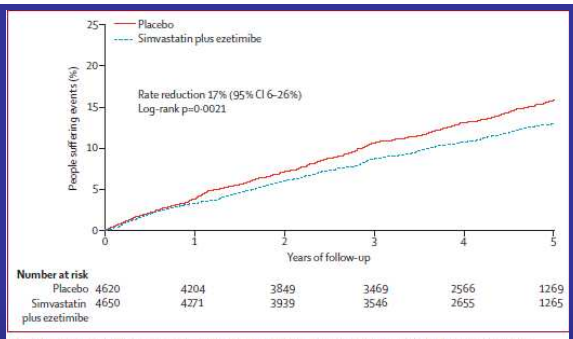
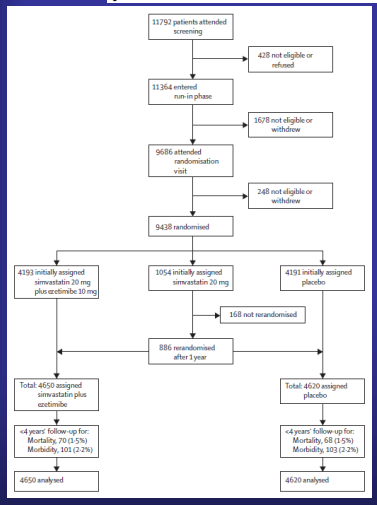


Figure 2: Life-table plot of effects of allocation to simvastatin plus ezetimibe versus placebo on major atherosclerotic events

Conclusion: Reduction of LDL cholesterol with simvastatin 20 mg plus ezetimibe 10 mg daily safely reduced the incidence of major atherosclerotic events in a wide range of patients with advanced chronic kidney disease. Studio SHARP

Lancet. 2011 June 9; 377(9784): 2181–2192.

The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial



	LDL-cholesterol-lowering drug use			LDL cholesterol difference (mmol/L)*		
	Simvastatin plus ezetimibe	Placebo	Absolute difference	Simvastatin plus ezetimibe	Placebo	Absolute difference (SE)
8–13 months	77%	3%	74%	−1·08	0·02	−1·09 (0·06)
26–31 months	71%	9%	61%	−1·00	−0·15	−0·85 (0·02)
44–49 months	68%	14%	55%	−0·84	−0·08	−0·77 (0·06)

*In patients initially allocated to simvastatin, no 1-year sample was collected, while samples scheduled for collection at 2·5 and 4 years were collected at 1·5 and 3 years after rerandomisation.

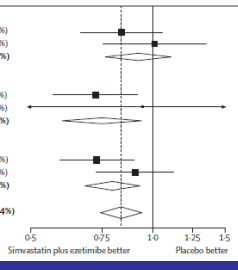
Table 2: **Average use of study simvastatin plus ezetimibe or non-study statin and average change in plasma LDL cholesterol from baseline, by period of follow-up**

Studio SHARP

Lancet. 2011 June 9; 377(9784): 2181–2192.

The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial

	Simvastatin plus ezetimibe (n=4650)	Placebo (n=4620)	Risk ratio (95% CI)	p value
Coronary events				
Non-fatal MI	134 (2·9%)	159 (3·4%)	0·84 (0·66–1·05)	0·12
CHD death	91 (2·0%)	90 (1·9%)	1·01 (0·75–1·35)	0·95
Subtotal: any major coronary event	**213 (4·6%)**	**230 (5·0%)**	**0·92 (0·76–1·11)**	**0·37**
Non-haemorrhagic stroke				
Ischaemic	114 (2·5%)	157 (3·4%)	0·72 (0·57–0·92)	0·0073
Unknown type	18 (0·4%)	19 (0·4%)	0·94 (0·49–1·79)	0·85
Subtotal: any non-haemorrhagic	**131 (2·8%)**	**174 (3·8%)**	**0·75 (0·60–0·94)**	**0·01**
Revascularisation procedures				
Coronary	149 (3·2%)	203 (4·4%)	0·73 (0·59–0·90)	0·0027
Non-coronary	154 (3·3%)	169 (3·7%)	0·90 (0·73–1·12)	0·36
Subtotal: any revascularisation	**284 (6·1%)**	**352 (7·6%)**	**0·79 (0·68–0·93)**	**0·0036**
Total: any major atherosclerotic event	**526 (11·3%)**	**619 (13·4%)**	**0·83 (0·74–0·94)**	**0·0021**



	Simvastatin plus ezetimibe (n=4650)	Placebo (n=4620)	p value
Muscle pain			
Any report	992 (21·3%)	960 (20·8%)	0·53
Study treatment stopped	49 (1·1%)	28 (0·6%)	0·02
Increased creatine kinase*			
>5 to ≤10 times ULN	50 (1·1%)	47 (1·0%)	0·86
>10 to ≤40 times ULN	17 (0·4%)	16 (0·3%)	1·00
>40 times ULN	4 (0·1%)	5 (0·1%)	0·99
Persistently increased transaminases†	30 (0·6%)	26 (0·6%)	0·71
Hepatitis			
Infective	12 (0·3%)	12 (0·3%)	1·00
Non-infective	6 (0·1%)	4 (0·1%)	0·76
No cause identified	3 (0·1%)	3 (0·1%)	1·00
Any hepatitis	21 (0·5%)	18 (0·4%)	0·76
Gallstones			
Complicated	85 (1·8%)	76 (1·6%)	0·55
Uncomplicated	21 (0·5%)	30 (0·6%)	0·25
Pancreatitis (without gallstones)	12 (0·3%)	27 (0·6%)	0·02

ULN=upper limit of normal. *Myopathy, defined as creatine kinase greater than ten times the ULN with muscle symptoms, occurred in nine (0·19%) versus five (0·11%) patients, of whom eight (0·17%) versus three (0·06%) were taking allocated treatment (and not taking any non-study statin) at the time of the event (both p=NS); for rhabdomyolysis, defined as myopathy with creatine kinase greater than 40 times the ULN (and hence included in counts of myopathies), the corresponding numbers were four (0·09%) versus one (0·02%) and four (0·09%) versus none, again both p=NS. †Consecutive increases of alanine or aspartate transaminase greater than three times the ULN.

Table 4: Effects of allocation to simvastatin plus ezetimibe on muscle and hepatobiliary system

Studio SHARP: -17% eventi aterosclerotici maggiori

Lancet. 2011 June 9; 377(9784): 2181–2192.

The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial

Panel: **Research in context**

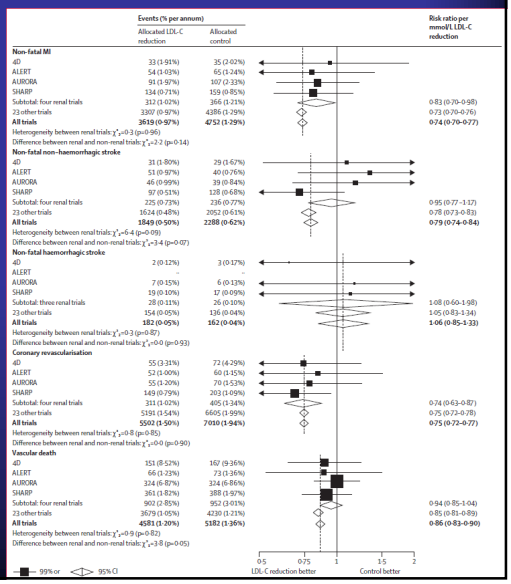
Systematic review

The Cholesterol Treatment Trialists' collaborative meta-analysis of individual participant data from 26 randomised trials[5] has shown that lowering LDL cholesterol with a statin regimen reduces the risk of myocardial infarction, coronary death, ischaemic stroke, and coronary revascularisation procedures by about a fifth per 1 mmol/L LDL cholesterol reduction in a wide range of people. However, none of the three trials[19–21] in patients with chronic kidney disease included in that meta-analysis reported a significant reduction in its primary vascular disease outcome, leading to uncertainty about whether lowering of LDL cholesterol is effective in renal patients.

Interpretation

The SHARP randomised trial has now shown that lowering of LDL cholesterol with simvastatin plus ezetimibe safely reduces the risk of major atherosclerotic events in a wide range of patients with chronic kidney disease. When the SHARP results are compared with those of the previous statin trials in renal patients, it appears that the absence of significant reductions in earlier trials could have been due both to the much smaller number and the much smaller proportion of vascular events in their primary outcomes that were related to atherosclerosis and, hence, preventable by lowering of LDL cholesterol.

Lancet. 2011 June 9; 377(9784): 2181–2192



Effect of fluvastatin on renal end points in the Assessment of Lescol in Renal Transplant (ALERT) trial

CONCLUSION:

The ALERT trial has established the benefits and safety of fluvastatin treatment for the prevention of cardiac morbidity and mortality in renal transplant recipients.

The present analysis of the ALERT trial showed no significant effect of fluvastatin on the prespecified renal end points of renal graft loss or doubling of serum creatinine.

Thus, early introduction of statin therapy after renal transplantation can be recommended for cardiac protection, but not for renal protection in general.

Kidney International, Vol. 66 (2004), pp. 1549–1555

Effect of fluvastatin on renal end points in the Assessment of Lescol in Renal Transplant (ALERT) trial

Table 3. Effect of fluvastatin treatment on incidence of renal end points in the ALERT study

No. of patients with end points	Incidence Fluvastatin ($N = 1050$)	Placebo ($N = 1052$)	RR	95% CI	P value[a]
Graft loss	146 (13.9)	137 (13.0)	1.055	0.835, 1.334	0.6520
Graft loss or doubling of serum creatinine	183 (17.4)	165 (15.7)	1.102	0.892, 1.361	0.3693
Graft loss or doubling of serum creatinine or death	276 (26.3)	268 (25.6)	1.02	0.86, 1.21	0.7893

RR, relative risk; CI, confidence interval.
[a]*P* values were determined by the Cox-Wald test.

Table 4. Change in glomerular filtration rate during follow-up

Visit	Fluvastatin ($N = 222$) N	Mean (SD)	Placebo ($N = 217$) N	Mean (SD)	Difference	P value
GFR *mL/min/1.73 m²*						
Baseline	222	52.9 (21.4)	217	52.1 (20.0)	−0.8	
18 months	191	51.5 (20.5)	185	49.3 (19.4)	−2.1	0.7571
36 months	178	50.5 (21.7)	172	49.6 (21.7)	−0.9	0.7545
60 months	130	46.0 (22.2)	114	47.1 (20.0)	1.0	0.8843
GFR by Cockcroft-Gault formula *mL/min/1.73 m²*						
Baseline	218	64.7 (24.4)	208	64.3 (19.3)	−0.8	
36 months	177	55.6 (19.1)	169	56.6 (18.8)	1.0	0.6235
60 months	128	55.2 (21.9)	110	59.2 (20.2)	4.0	0.5156

GFR, glomerular filtration rate.

Kidney International, Vol. 66 (2004), pp. 1549–1555

Kidney International, Vol. 66 (2004), pp. 1549–1555

Effect of fluvastatin on renal end points in the Assessment of Lescol in Renal Transplant (ALERT) trial

Table 2. Renal transplant characteristics of intention to treat population at baseline

	Fluvastatin ($N = 1050$)	Placebo ($N = 1052$)
First transplantation *N* (%)	894 (85.1)	900 (85.6)
Recipient age at last transplantation *years*	44.3 (11.3)	44. 8 (11.4)
Time since last transplantation *years*	5.2 (3.4)	5.2 (3.4)
Rejections since last transplantation *N* (%)	454 (43.2)	448 (42.6)
Cold ischemia time *hours*	19.8 (7.6)	19.7 (7.9)
Delayed graft function (DGF)	180 (17.1)	185 (17.6)
Donor age *years*	40.2 (15.2)	40.9 (15.4)
No HLA-DR mismatches *N* (%)	336 (32.1)	326 (31.0)
Panel-reactive antibodies positive *N* (%)	163 (15.5)	164 (15.6)
Treatment for CMV *N* (%)	148 (14.1)	138 (13.1)
Total months on renal replacement therapy	88.5 (56.5)	88.8 (58.3)
Type of last transplantation *N* (%)		
Live donor	240 (22.9)	229 (21.8)
Cadaveric donor	809 (77.0)	822 (78.1)
Serum creatinine *μmol/L*	147 (54.4)	143 (51.0)
Urinary protein *g/24h*	0,5 (1.4) [$N = 753$]	0,4 (0.7) [$N = 770$]
Urinary albumin *g/24h*	0,3 (0.8) [$N = 298$]	0,2 (0.5) [$N = 270$]
Creatinine clearance *mL/min*	60,2 (20.8) [$N = 1007$]	60,3 (20.7) [$N = 1003$]

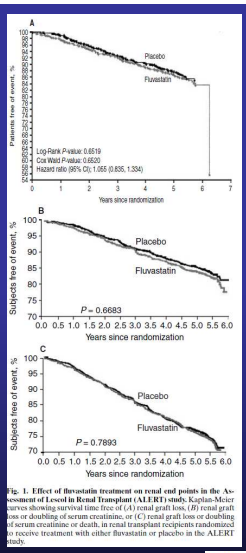


Fig. 1. Effect of fluvastatin treatment on renal end points in the Assessment of Lescol in Renal Transplant (ALERT) study. Kaplan-Meier curves showing survival time free of (*A*) renal graft loss, (*B*) renal graft loss or doubling of serum creatinine, or (*C*) renal graft loss or doubling of serum creatinine or death, in renal transplant recipients randomized to receive treatment with either fluvastatin or placebo in the ALERT study.

Kidney International, Vol. 66 (2004), pp. 1549–1555

Effect of fluvastatin on renal end points in the Assessment of Lescol in Renal Transplant (ALERT) trial

CONCLUSION

The ALERT trial has established the benefits and safety of fluvastatin treatment for the prevention of cardiac morbidity and mortality in renal transplant recipients. The present analysis of the ALERT trial showed no significant effect of fluvastatin on the prespecified renal end points of renal graft loss or doubling of serum creatinine. Thus, early introduction of statin therapy after renal transplantation can be recommended for cardiac protection, but not for renal protection in general.

Kidney International, Vol. 66 (2004), pp. 1549–1555

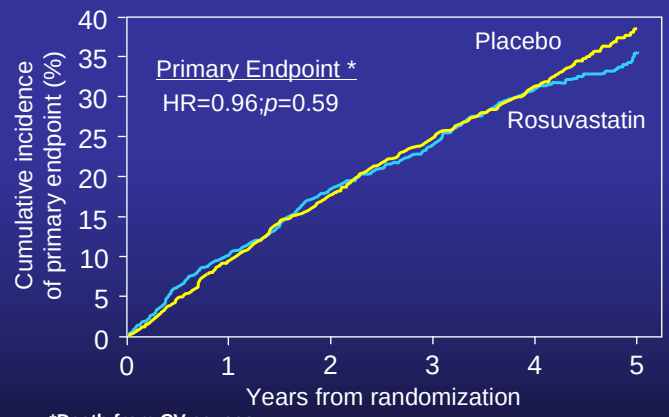
Rosuvastatin and Cardiovascular Events in Patients Undergoing Hemodialysis

In conclusion, the AURORA trial evaluated the effect of rosuvastatin on cardiovascular events in a population of patients with end-stage renal disease. Despite significantly reducing the levels of LDL cholesterol and high-sensitivity C-reactive protein, treatment with rosuvastatin was not associated with a reduction in the combined end point of myocardial infarction, stroke, or death from cardiovascular causes.

- n engl j med 360;14 nejm.org april 2, 2009

Rosuvastatin and CV events in haemodialysis patients: AURORA trial

- 2776 patients on haemodialysis ≤ 2 years; 26% with DM; 40% with prior CVD; 15% PAD
- Baseline lipids: LDL-C 2.6 mmol/L;TG 1.78 mmol/L
- Rosuva 10mg vs Pbo x 3.8 yrs; Δ LDL-C: 1.05 mmol/L



*Death from CV causes, non-fatal MI, or non-fatal stroke

Fellström BC et al. N Engl J Med 2009; 360:1395-407

Rosuvastatin and Cardiovascular Events in Patients Undergoing Hemodialysis

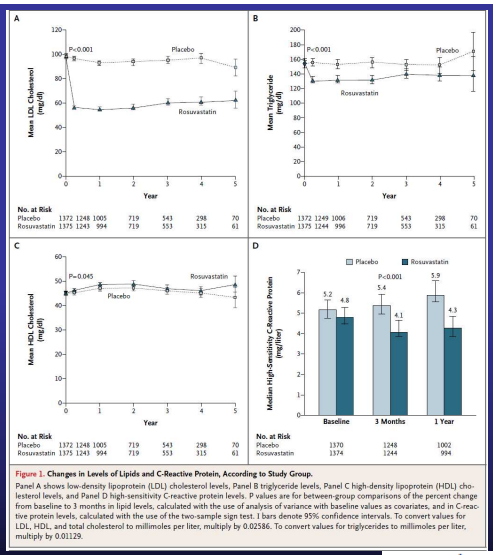


Figure 1. Changes in Levels of Lipids and C-Reactive Protein, According to Study Group.

Panel A shows low-density lipoprotein (LDL) cholesterol levels, Panel B triglyceride levels, Panel C high-density lipoprotein (HDL) cholesterol levels, and Panel D high-sensitivity C-reactive protein levels. P values are for between-group comparisons of the percent change from baseline to 3 months in lipid levels, calculated with the use of analysis of variance with baseline values as covariates, and in C-reactive protein levels, calculated with the use of the two-sample sign test. I bars denote 95% confidence intervals. To convert values for LDL, HDL, and total cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129.

N Engl J Med 2009;360:1395-407

Rosuvastatin and Cardiovascular Events in Patients Undergoing Hemodialysis

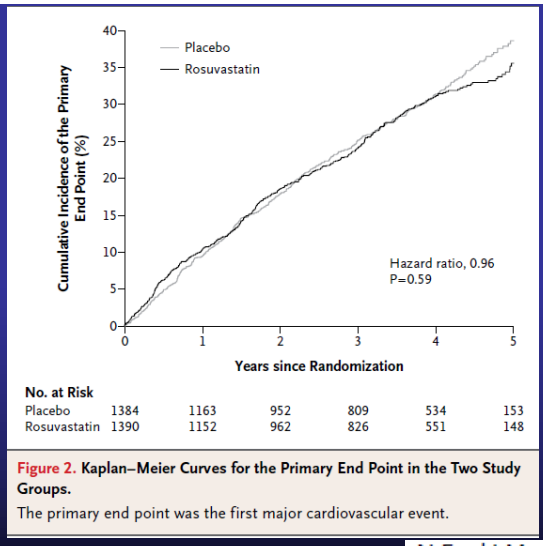


Figure 2. Kaplan–Meier Curves for the Primary End Point in the Two Study Groups.
The primary end point was the first major cardiovascular event.

N Engl J Med 2009;360:1395-407

Aurora: Primary endpoint

Endpoint	Placebo (n=636)	Rosuvastatin (n=619)	RR (95% CI)
Primary endpoint	408	396	0.96 (0.84-1.11)*
Cardiac death	324	324	
Non-fatal MI	107	91	
Fatal stroke	21	23	
Non-fatal stroke	45	53	

* *P*=0.59

Fellström BC et al. N Engl J Med 2009; 360:1395-407

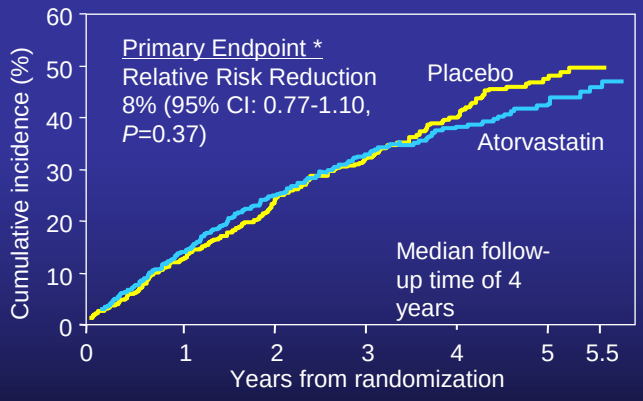
Rosuvastatin and Cardiovascular Events in Patients Undergoing Hemodialysis

In conclusion, the AURORA trial evaluated the effect of rosuvastatin on cardiovascular events in a population of patients with end-stage renal disease. Despite significantly reducing the levels of LDL cholesterol and high-sensitivity C-reactive protein, treatment with rosuvastatin was not associated with a reduction in the combined end point of myocardial infarction, stroke, or death from cardiovascular causes.

N Engl J Med 2009;360:1395-407

Atorvastatin in Type 2 diabetics on dialysis: **4D Study**

- **1255 T2DM patients on dialysis for 8.3 mo; 29% with prior MI or revascularization or CHD; 35% CHF; 45% PAD**
- **Baseline lipids: LDL-C 3.2 mmol/L;TG 3.0 mmol/L**
- **Atorva 20mg vs Pbo x 4 yrs; Δ LDL-C: 1 mmol/L**



***Primary EP: CV death, non fatal MI, stroke**

Wanner C et al. N Engl J Med 2005; 353:238-48

4D: Primary endpoint

Endpoint	Placebo (n=636)	Atorvastatin (n=619)	RR (95% CI)
Primary endpoint	243	226	0.92 (0.77-1.10)*
Cardiac death	149	121	
Non-fatal MI	79	70	
Fatal stroke	13	27	
Non-fatal stroke	32	33	

* *P*=0.37

Wanner C et al. N Engl J Med 2005; 353:238-48

Atorvastatin in Patients with Type 2 Diabetes Mellitus Undergoing Hemodialysis

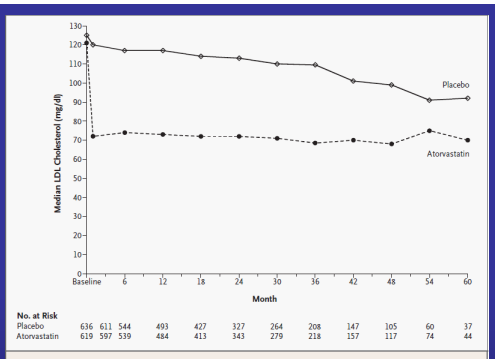


Figure 2. Median Level of Low-Density Lipoprotein (LDL) Cholesterol from Baseline to the End of the Study.
To convert values for LDL cholesterol to millimoles per liter, multiply by 0.02586.

Table 2. Rates of Primary and Secondary End Points.[a]

End Point	Placebo Group (N=636)	Atorvastatin Group (N=619)	RR (95% CI)	P Value
	no. (%)			
Primary	243 (38)	226 (37)	0.92 (0.77–1.10)	0.37
Death from cardiac causes	149 (23)	121 (20)	0.81 (0.64–1.03)	0.08
Sudden death	83 (13)	77 (12)		
Fatal myocardial infarction	33 (5)	23 (4)		
Death due to congestive heart failure	24 (4)	17 (3)		
Death after interventions to treat coronary heart disease	4 (0.6)	3 (0.5)		
Other death due to coronary heart disease	5 (0.8)	1 (0.2)		
Nonfatal myocardial infarction	79 (12)	70 (11)	0.88 (0.64–1.21)	0.42
Silent	50 (8)	41 (7)		
Nonsilent	35 (6)	33 (5)		
Fatal stroke	13 (2)	27 (4)	2.03 (1.05–3.93)	0.04
Ischemic	7 (1)	18 (3)		
Hemorrhagic	5 (0.8)	3 (0.5)		
Other (not classified)	1 (0.2)	6 (1)		
Nonfatal stroke	32 (5)	33 (5)	1.04 (0.64–1.69)	0.89
Secondary				
All cardiac events combined	246 (39)	205 (33)	0.82 (0.68–0.99)	0.03
Death from cardiac causes	149 (23)	121 (20)		
Nonfatal myocardial infarction	79 (12)	70 (11)		
PTCA	45 (7)	34 (5)		
CABG	30 (5)	24 (4)		
Other interventions to treat coronary heart disease	0	1 (0.2)		
All cerebrovascular events combined	70 (11)	79 (13)	1.12 (0.81–1.55)	0.49
Stroke	44 (7)	59 (10)	1.33 (0.90–1.97)	0.15
Ischemic	33 (5)	47 (8)		
Hemorrhagic	8 (1)	5 (1)		
Other (not classified)	6 (1)	10 (2)		
TIA or PRIND	31 (5)	26 (4)		
Death from all causes	320 (50)	297 (48)	0.93 (0.79–1.08)	0.33
Death from causes other than cardiovascular or cerebrovascular disease	158 (25)	149 (24)	0.95 (0.76–1.18)	0.62
Fatal infection	68 (11)	60 (10)		
Fatal cancer	19 (3)	17 (3)		
Other	71 (11)	72 (12)		

Conclusions: Atorvastatin had no statistically significant effect on the composite primary end point of cardiovascular death, nonfatal myocardial infarction, and stroke in patients with diabetes receiving hemodialysis.

Analysis of Studies evaluating CVD in CKD populations 4D, ALERT, AURORA, SHARP

	Treatment & Follow-up	Primary Endpoint	RR	*p*
4D (1255 Dialysis pat.)[1]	Atorva 20mg 4 years	Cardiac death, non fatal MI and stroke	0.92 (0.77 – 1.10)	p=0.37
ALERT (2102 Trans-plant pat.)[2]	Fluva 40-80mg 5 years	Cardiac death, non fatal MI and coronary interv. procedure	0.83 (0.64 – 1.06)	p=0.139
AURORA (2776 Dialysis pat.) [3]	Rosuva 10mg 3.8 years	CV death, non fatal MI and non fatal stroke	0.96 (0.84-1.11)	p=0.59
SHARP (9438 Pre & dialysis pat.)*	Simva 20-Eze 10 mg 4.9 years	Coronary death, MI, ischemic stroke, or revascularization	0.83 (0.74- 0.94)	p=0.0022

1 Wanner C et al. *N Engl J Med.* 2005;353(3):238–248

2 Holdaas H et al. *Lancet.* 2003;361(9374):2024–2031

3 Fellström BC et al. *N Engl J Med.* 2009;360(14):1395-1407

* www.SHARPinfo.org

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Therapeutic considerations when using common therapies in patients with diabetes with varying degrees of renal impairment

Lipid Lowering Therapies

	CKD 1 & 2 eGFR ≥60 mL/min	CKD 3 eGFR 30-59 mL/min	CKD 4 eGFR 15-29 mL/min	CKD 5 eGFR <15 mL/min or dialysis
Bile Acid Sequestrant				
Cholestyramine	No dose adjustment			
Cholesterol Absorption Inhibitor				
Ezetimibe	No dose adjustment			
Nicotinic Acid (niacin)	No dose adjustment	50% of total daily dose administered as divided doses		25% of total daily dose administered in divided doses

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Fibrates	*Risk of rhabdomyolisis when fibrates used in combination with statins is increased in CKD and, therefore, combination should be avoided.*				
Bezafibrate	No dose adjustment	Use alternative agent			
Fenofibrate	No dose adjustment	Reduce dose		Use alternative agent	Fenofibrate micronized should not be used as initial treatment in CKD. Initiate with Lipidil EZ 48 mg/day.
Gemfibrozil	No dose adjustment	Use alternative agent			Concomitant use of gemfibrozil and repaglinide should be avoided as can result in hypoglycemia.

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Statins				
Atorvastatin		Manufacturer recommends lowest dose (10 mg once daily) be used		Plasma concentrations are similar to those with normal renal function, but several cases of rhabdomyolysis reported in patients with renal insufficiency.
Fluvastatin	No dose adjustment		Not recommended	Recommendation from manufacturer is based on lack of experience rather than renal excretion.
Lovastatin	No dose adjustment		Use low dose (max dose 20 mg/day)	10% renal elimination. Doubling of plasma concentration in moderate to severe renal impairment.
Pravastatin		Use lowest dose as precautionary measure		Lack of data. 20% renal elimination.
Rosuvastatin	No dose adjustment		Use low dose (max dose 10 mg/day)	10% renal elimination.
Simvastatin	No dose adjustment		Use low dose (max dose 10 mg/day)	13% renal elimination.

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Neuropathy Therapies				
Anticonvulsants				
Gabapentin	Max 3600 mg/ day divided tid	Max 1400 mg/ day divided bid	Max 700 mg/ day given once daily	Max 150-300 mg/day given once daily	Hemodialysis supplemental dosing required: 125-350 mg after each 4 hours of hemodialysis.
Pregabalin	Max 600 mg/ day divided bid or tid	Max 300 mg/ day divided bid or tid	Max 150 mg/day given once daily or bid	Max 75 mg/day given once daily	Hemodialysis supplemental dosing required.

Pharmacokinetics of Pregabalin in Subjects with Various Degrees of Renal Function

Pregabalin dosage adjustment should be considered for patients with CLcr < 60 mL/min. A 50% reduction in pregabalin daily dose is recommended for patients with CLcr between 30 and 60 mL/min compared to those with CLcr > 60 mL/min. Daily doses should be further reduced by approximately 50% for each additional 50% decrease in CLcr. Pregabalin was highly cleared by hemodialysis. Supplemental pregabalin doses may be required for patients on chronic hemodialysis treatment after each hemodialysis treatment to maintain steady-state plasma pregabalin concentrations within desired ranges.

J Clin Pharmacol. **2003 Mar;43(3):277-83**

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Erectile Dysfunction Therapies				
Phosphodiesterase-5 (PDE-5) Inhibitors				
Sildenafil	No dose adjustment		Reduce starting dose to 25 mg	
Tadalafil		10-20 mg (max frequency of alternate days and not more than 3 times per week)		2.5-5 mg once a day may be considered in CKD stage 3 but daily dosing is not recommended in CKD stage 4 and 5.

Compromissione della funzionalità renale Levitra (Vardenafil
Non è necessario modificare la dose nei pazienti con compromissione della funzionalità renale da lieve a moderata. Nei pazienti con grave compromissione della funzionalità renale (clearance della creatinina <30 ml/min), si deve prendere in considerazione una dose iniziale di 5 mg. In base alla tollerabilità e all'efficacia, la dose può essere aumentata a 10 mg e successivamente a 20 mg.

ACC/AHA Expert Consensus Document

Use of Sildenafil (Viagra) in Patients With Cardiovascular Disease

Summary Table of Clinical Recommendations

A. Use of Viagra clearly contraindicated
   1. Concurrent use of nitrates (see Appendix A)

B. Cardiovascular effects of Viagra may be potentially hazardous (use dependent on individual clinical assessment)
   1. Patients with active coronary ischemia who are not taking nitrates (eg, positive exercise test for ischemia)
   2. Patients with congestive heart failure and borderline low blood pressure and borderline low volume status
   3. Patients on a complicated, multidrug, antihypertensive program
   4. Patients taking drugs that can prolong the half-life of Viagra (see Appendix B)

Renal Dysfunction

Patients with severe renal impairment (creatinine clearance, 30 mL/min) have a reduced clearance of sildenafil. Plasma levels of the parent drug and of its metabolites in patients with severe renal impairment are approximately twice those found in healthy subjects. Particular care should be taken in the administration of concomitant medications that may lower blood pressure in patients receiving sildenafil whose renal function is severely impaired. There were no significant effects on the metabolism of sildenafil seen in subjects with mild (creatinine clearance 50 to 80 mL/min) or moderate (creatinine clearance 30 to 49 mL/min) renal impairment

Grazie per l'attenzione