Munich, Germany - Results of two related trials investigating the effects of statins on urinary protein excretion and kidney function suggest that atorvastatin (Lipitor, Pfizer) may be protective but that rosuvastatin (Crestor, AstraZeneca) seems to have no protective effects and in fact may be harmful [1]. The different effects were seen in both diabetic and nondiabetic patients.

High-dose atorvastatin significantly reduced proteinuria and did not affect renal function, whereas rosuvastatin was associated with a significant decline in function and had no effect on proteinuria, according to the results of the Prospective Evaluation of Proteinuria and Renal Function in Diabetic Patients With Progressive Renal Disease (PLANET I) and Prospective Evaluation of Proteinuria and Renal Function in Nondiabetic Patients With Progressive Renal Disease (PLANET II) trials, reported in a late-breaking trials session here at the 2010 European Renal Association-European Dialysis and Transplant Association Congress by Dr Dick de Zeeuw (University Medical Center in Groningen, the Netherlands).

In diabetic and nondiabetic patients, proteinuria is a risk factor for further loss of kidney function and progression to end-stage renal disease. Experimental results have suggested that statins reduce proteinuria and preserve kidney function, but clinical studies have produced mixed results.

The two randomized double-blind multinational PLANET trials tested the effects of atorvastatin 80 mg/day or rosuvastatin 10 or 40 mg/day on urinary protein excretion and renal function in hypercholesterolemic patients with moderate proteinuria.

PLANET I involved 325 patients with type 1 or 2 diabetes, and PLANET II involved 220 patients without diabetes. Patients had urinary protein/creatinine ratios of 500 to 5000 mg/g, a fasting LDL-cholesterol level of 90 mg/dL or higher, and had used ACE inhibitors or angiotensin-receptor blockers (ARBs) for at least three months prior to screening.

There was an eight-week lead-in period, and then patients were put on the drug. The patients randomized to receive rosuvastatin 40 mg/day or atorvastatin 80 mg/day took half the daily dose for the first four weeks and then escalated to full doses.

Patients with severe renal disease, defined as an estimated glomerular filtration rate (eGFR) below 40 mL/min per 1.73 m², or PLANET I patients with a hemoglobin A1c level above 11% were excluded from the study, as were people with active liver disease.

The primary end point of the studies was change in urinary protein/creatinine ratio from baseline to week 52 or to the last on-treatment observation carried forward. For PLANET I (diabetic patients), de Zeeuw summarized: "Atorvastatin significantly reduces the proteinuria in these patients on top of ACE/ARB therapy, with around a 15% reduction in proteinuria, whereas rosuvastatin, both 10 and 40 mg, had no significant effect at all on proteinuria."

The effect of atorvastatin was evident by week 26 and continued through week 52, but neither rosuvastatin dose lowered proteinuria at either time point.

In PLANET II (the nondiabetic cohort), "we see a similar pattern, even more pronounced," he said. Atorvastatin reduced proteinuria by more than 20% at 26 and 52 weeks, but there was no significant effect with either dose of rosuvastatin. The results for albuminuria were very similar to those for proteinuria.

For eGFR, de Zeeuw said the results were "very surprising," in that in the PLANET I trial, patients on rosuvastatin lost more kidney function over 52 weeks than did those on atorvastatin. Patients on atorvastatin lost about 1 to 2 mL/min per 1.73 m² over 52 weeks, those on rosuvastatin 10 mg/day lost about 4 mL/min per 1.73 m², and those on rosuvastatin 40 mg/day lost dose to 8 mL/min per 1.73 m².

In nondiabetic patients (PLANET II), the effects of the treatments on kidney function were slightly less pronounced. There was a significant decline in eGFR with rosuvastatin 40 mg/day but not in the other two treatment groups.

De Zeeuw explained that the differential effects on proteinuria and eGFR in the treatment groups was not a result of differences in lipid lowering. All the treatments lowered total and LDL cholesterol, and there were no significant differences in the amount of lipid lowering.

All the treatments were well tolerated in both trials. A total of six deaths occurred, and all were reported as not of a renal etiology. Although determined by investigators to be not related to drug, the incidence of renal adverse events was higher in the rosuvastatin 40 mg/day group in PLANET I.
but not in PLANET II.

**PLANET I: Summary of renal adverse events (%)**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Rosuvastatin 10 mg/day (n = 116)</th>
<th>Rosuvastatin 40 mg/day (n = 123)</th>
<th>Atorvastatin 80 mg/day (n = 110)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any renal adverse event</td>
<td>7.8</td>
<td>9.8</td>
<td>4.5</td>
<td>NS</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>0.0</td>
<td>4.1</td>
<td>0.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Serum creatinine doubling</td>
<td>0.0</td>
<td>4.9</td>
<td>0.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Serum creatinine doubling or acute renal failure</td>
<td>0.0</td>
<td>7.3</td>
<td>0.9</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

To download table as a slide, click on slide logo above

One limitation of the study was that there was no placebo control group; ethical committees overseeing the study would not allow the investigators to have a no-statin group, "which was quite a surprise to us, because I think there is no proof yet that statins actually help in these patients," de Zeeuw said.

He concluded from these findings that in diabetic and nondiabetic patients with proteinuria, using optimal therapy, including ACE inhibitors and ARBs:

- **Atorvastatin 80 mg/day significantly reduced proteinuria by about 20%.**
- Rosuvastatin 10 or 40 mg/day had no effect on proteinuria.
- Rosuvastatin 40 mg/day was associated with a significant decline in eGFR of about 8 mL/min per 1.73 m² per year.
- **Atorvastatin 80 mg/day had no effect on eGFR.**
- **Atorvastatin 80 mg/day has a clear advantage over rosuvastatin 40 mg/day in terms of renal protection and renal damage.**

After many trials and many years of statin use, cardiologists have largely concluded that most of the lipid effects they see with statins are a class effect and not necessarily unique to any particular one. However, de Zeeuw said this trial "sort of dismembers the class effect," at least for the parameters studied here. Atorvastatin and rosuvastatin were obviously exerting different effects on proteinuria and renal function. One big question remaining is whether atorvastatin is actually protecting the kidneys or whether rosuvastatin is damaging them. Based on the current results, de Zeeuw advised, "If you are considering putting such a patient on a statin, you should not put them on rosuvastatin."

Taking the two PLANET trials together, Dr David Harris (University of Sydney, Australia) said: "It's a very important study because it has dispelled the idea about class effects of statins and has shown that two drugs that we thought were extremely similar have very different effects and, clinically, very significant effects on kidney disease. . . . It certainly would point any practicing nephrologist toward using atorvastatin rather than the other drug in this situation."

But he noted that until there are data on hard end points, such as patients progressing to dialysis or dying, the full story on these drugs in this setting will not be known.

The ongoing Study of Heart and Renal Protection (SHARP) trial with simvastatin and ezetimibe (Zetia, Merck) may provide some answers. The trial is studying whether lowering blood cholesterol using simvastatin and ezetimibe in combination or simvastatin alone is better than placebo for reducing risk of cardiovascular events or delaying the need for dialysis in patients with kidney disease. Data collection is scheduled to complete in late summer 2010.

The PLANET trials were funded by AstraZeneca. de Zeeuw reports being a consultant to and receiving honoraria (to his institution) from Abbott, Amgen, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Hemocue, Novartis, N oxsein, Merck Sharp & Dohme, and Johnson & Johnson. Harris has disclosed no relevant financial relationships.

The complete contents of Medscape Medical News, a professional news service of WebMD, can be found at www.medscape.com, a website for medical professionals.

**Related links**

- Albuminuria developing, progressing, despite treatment with ACE inhibitors or ARBs (Brain/Kidney/Peripheral > Brain/Kidney/Peripheral; Jul 02, 2010)
- Role of kidney disease on CV outcomes underappreciated (Brain/Kidney/Peripheral > Brain/Kidney/Peripheral; Apr 09, 2010)
- Statins reduce the risk of cardiovascular events in patients with kidney disease and diabetes (Lipid/Metabolic > Lipid/Metabolic; Oct 26, 2005)
- 4D trial published: No benefit of atorvastatin in patients with diabetes undergoing hemodialysis (Lipid/Metabolic > Lipid/Metabolic; Jul 21, 2005)
- ALERT, 4D: Mixed results seen with statins in different renal populations
Your comments

PLANET I and II: Atorvastatin beats rosuvastatin for protecting kidneys in diabetic and nondiabetic patients

# 1 of 30
July 6, 2010 09:29 (EDT)
Dmitri Vasin

Fascinating...
Add to this CORONA and GISSI-HF where Rosuva had clear trend towards improvement in renal function vs TNT where both 10 and 80 mg Atorva was associated with improvement in renal function (10 more than 80) and indeed class effect concept with regard to statins effect on renal function starts to look very shaky.
Can also add to this:
STENO-2 where Atorva was used - 85% reduction in ESRD
GREACE - also used Atorva...
Renal remission clinic protocols (Ruggenenti, Remuzzi)also use Atorva.
Considering Atorva is going generic next year and most patients nowadays needing 2+ drugs lipid lowering therapy I see little reason to use Rosuva, unless head to head outcome studies show better hard endpoint outcomes.

# 2 of 30
July 6, 2010 11:46 (EDT)
CJ McConnell

And in 4D, fatal ischemic stroke increased 201% in ESRD patients.
How often did Pfizer detail that large dialysis patient study from Europe?

# 3 of 30
July 6, 2010 03:27 (EDT)
Michael Cobble, M.D.

Or I guess
You could use rosuva if atorva failed which we see quite often. Steno2 as you know was multifactorial tx with ace/arb/asa/glucose and atorva was just the statin used. Uncertain why ASPEN showed no benefit for those pts with DM2 (perhaps they didn't have enough MA for benefit). We still use whatever statin it takes to reach LDLc, HDLc, ApoB goals. Start generic and go branded if not to goal in 3 months.

# 4 of 30
July 6, 2010 10:06 (EDT)
CJ McConnell

That's reasonable Dr. C,
Rosuva has several desirable characteristics not available with Atorva. Once generic, I would rather titrate up on Advicor or Simcor or Niaspan / gen-simva combo vs. deal with the atorva baggage. Dr. Bale is not a big atorva fan either.

# 5 of 30
July 7, 2010 10:29 (EDT)
Dmitri Vasin

Are you confusing features (of rosuva) with benefits (of Atorva)?
In absence of outcome data (or rather presence of negative ones) rosuva is a nicely loaded car with power windows and heated side mirrors that does not have an engine...
Rosuva in AURORA increased non-fatal strokes 17% and had overall increased in fatal and all strokes.
Post hoc of 4d showed mortality benefit in patients with mid-range elevated CRP. AURORA has not shown it to date.
Atorva has SPARCL and TNT to show stroke reduction in morbid population.
Rosuva had very visible failures in GISSI-HF (23% increase)and CORONA. We can continue forever at this pace. I am not sold on Rosuva features (especially lack of renal protection and proteinuria improvement) and would like to see benefits before I subject my patients to it. I will stick with my used Honda and let others chance of being stranded on the side of the road in their new Cadillacs... Problem is that it is not prescribers, but patients who ended up stranded.
UKPDS (and ACCORD, I believe) failed to show renal function preservation with either with tighter BG or BP control. Thus, missing ingredient in STENO-2 was Atorva...unless you presume that there is a magic in the two former when applied together.

# 6 of 30
July 7, 2010 02:35 (EDT)
D D

Dr. Bale?!?
You can't be serious...you're aligning your choice of statins with an overated FP? Vasin lists so many pro's of atorva, and you still manage to say it has baggage vs. rosuva? I'd take the evidence associated with atorva vs. the 4+ failed trials for rosuva any day.

# 7 of 30
July 7, 2010 04:09 (EDT)
Atorvastatin beats rosuvastatin for kidneys | theheart.org

DV

Dmitri the vodka is pickling your brain and the cheap beer is pickling mine. I like all statins (we use them all) I don’t think cadillac and honda and car features quite fairly describe these agents. We use the lipid agent that safely gets pts to lipid goals. Simcor would be my favorite as well followed by simva then rosuva. People forget it took pfizer nearly 7 years to show outcome benefit. AZ has been robust with evidence and outcomes studies in many populations. Who would do large outcomes trials in AS with statin or CHF with statin or post stroke with statin. Gizzi was unique as the CHF group had much higher nonischemic CHF than is seen in ‘normal’ patient populations. I like atorva. One could name many failed studies with this product, but of course not as many as PFE has never been one to do many studies. It’s a mixed bag as you can’t please all parties and you place yourself at risk if a study fails or fails to publish. One thing I have always liked about AZ is they are open and honest when results fail or succeed. One can’t compare studies, that would be like comparing CDP with 45S with VAHIT with FIELD. Different populations and demographics. Again why would atorva fail in ASPEN and why wouldn’t PFE present that data proactively to balance the other atorva studies. Don’t forget Atorva ARR was 1% with NNT like JUP.

# 8 of 30

July 7, 2010 04:13 (EDT)

Michael Cobble, M.D.

PS

You’re driving that KIF6 cadillac. I like the evidence but it shouldn’t trump guidelines which Celera has been promoting. KIF6 negative sprinkle the statin (don’t worry about LDL) target other lipid issues.’ What evidence supports that? Not to say it won’t ever do that. Would KIF testing help in JUPITER or FIELD or ACCORD? It might. Would it be worth the cost? It might. s LPA genotyping worth the cost or just have all high risk pts on aza? Should all primary DM2 pts included under 130). Yes I think it would have been very powerful to see atorva 40 considered a low risk population with LDL just over 100 (target would have high risk CAD pts to LDL goal under 70 is powerful. JUP as you know was efficacy) compared to what i was trained with 20 years ago. TNT was a no trial could have considerable repercussions for AZ

# 9 of 30

July 7, 2010 05:01 (EDT)

D Hackam

statin trials

Fluvastatin failed in ALERT. Atorvastatin failed in ASPEN, 4D, IDEAL. Rosuvastatin failed in CORONA, GISSI-HF, AURORA. Pravastatin failed in ALLHAT-LAA. Simvastatin failed in SEAS, A to Z, SEARCH. Every statin has at least one or more neutral or negative trials. This does not refute the overwhelming evidence from this class as a whole, whether looked at individually or in aggregate (meta-analysis; your favourite). No statin - including rosuva - has overwhelmingly negative/neutral outcome data and thus should be avoided. But if I get renal failure on my crestor, I shall switch to lipitor (which is hepatically cleared).

# 10 of 30

July 7, 2010 06:00 (EDT)

Glen Brizendine

Failed trials and such

Entertaining discussion to be sure. However to be factual -- 1 of the failed Atorva trials had control arm with >25% lipid agent usage usage and 1 had no study statin usage in the control arm of 15% --- and MC, 1 of the failed trials you mention IDEAL, had a control arm that was 100% statin. The failed trials from the "other potent statin" and their 1 successful trial have one thing in common -- they were all placebo controlled trials. With respect - factually, atorva has an outcomes trial within 4 years of FDA approval but since the "experts" were not the PI's and a major journal did not publish, I suppose it does not count although the results were "shockingly" similar to results seen later in similar pt type but published in NEJM, therefore more "valid". As for PFE "never being ones to do many studies" -- ASCOT,CARDS,TNT,4D,IDEAL,SPARC,ASPEN,ALLIANCE,AVERT,MIRACL just the hard endpoint trials, 3 of which were against ACTIVE treatment not PLACEBO because the folks at PFE must believe that if the medical community knows nothing at all they certainly know that PLACEBO doesn't work anymore. So why do we continue to be subjected to placebo controlled statin trials? If the folks in the AZ clinical development division are to be held in such respect isn't it time (after that clinicains demand a trial pitting their agent against something other than placebo? Just sayin'

DISCLOSURE -industry affiliation

# 11 of 30

July 7, 2010 07:51 (EDT)

Michael Cobble, M.D.

industry

it was just interesting for us to see atorva become number one statin before hard outcomes, amlodipine number on ccb without hard outcomes. a company that has great products but even better buying power and marketing. Of course i'm not anti industry, the products today are so much better (safety and efficacy) compared to what i was trained with 20 years ago. TNT was a no brainer, your drug against your drug, but great evidence to show treating very high risk CAD pts to LDL goal under 70 is powerful. JUP as you know was considered a low risk population with LDL just over 100 (target would have been under 130). Yes I think it would have been very powerful to see atorva 40 vs. rosuva 20 vs. placebo in that study. I only wish AZ and PFE would have collaborated on such or persuaded something similar. All the best.

# 12 of 30

July 8, 2011 11:51 (EDT)

evan levine

Trial could have considerable repercussions for AZ

Lipitor going generic plus above results suggests that AZ is in huge trouble. After reviewing these findings I will, if the jerks that run the prescription drug plans allow me to, reach for Lipitor before Crestor. Having said that , at four bucks a month, Zoor remains the best first choice.
$4/mos
Zocor is $25/mos in our area at walmart I have seen prices near $70/mos at other pharmacies. Unfortunately generic doesn’t mean cheap.

As the ‘Last Man Standing” in the on-patent/statin market,… Rosuvastatin still has cache over atorvastatin… unless you only look at a Friedewald LDL,… If… we reach for a generic… simvastatin is top of the list… not even after atorvastatin goes generic. Fluvastatin is safe for use with gemfibrozil… we avoid fenofibrate… no outcomes data; Simvastatin 10–20 with 1500–2000 mg of ER or IR niacin,… completely dominates ApoB/LDL “cache” Pfizer pushed down our throats. Atorvastatin stinks on pattern conversion, HDL2[b], and worst of all, it increase Lp(a),… so why use it at all. On or Off patent…

renal signal needs to be clarified
No doubt this renal signal needs to be clarified, as it applied not just to proteinuria/GFR (which are gross surrogates) but also to acute renal events. This is reminiscent of the peri-registration controversy pertaining to tubular proteinuria and hematuria when crestor was first approved. A meta-analysis of the data from jupiter, planet I/II, gissi-hf, and corona would probably shed a bit more light on this issue.

All statins are not created equal
Just from personal experience, when I was started on 10 mg lipitor, within a month both ALT and AST were elevated by 50%. When I was switched to 10 mg zocor, liver enzymes were fine. Unfortunately, 10 years of low dose zocor could not prevent coronary artery disease. Now I am no 20 mg crestor or 2 g niacin with no issues wrt to liver enzymes. Muscle ache is also minimal. There appear to be idiosyncratic effects with these statins and in my case trial and error led to rosuvastatin. Also with combination therapy, I would rather be on a lower dose of a more potent statin.

Should there be a Crestor 40?
Considering the rather remarkable incidence of renal compromise with Crestor 40, should this dosage still be used?
RE: #19 Market leader over-rated??

Then by all means shouldn't the medical community demand a head to head trial between the 2 potent statins be conducted? If it was so frustrating that the current market leading statin gained major market share against simva with no head to head outcomes data then why was the same thing allowed to happen again? Why wasn't there a "rising up" to demand a head to head by the new comer with supposed "vast" HDL advantages (which BTW have never been duplicated in large, DBPCKT ie. Coro,n,Jupiter)? I know why... because clinicians in large part don't differenitiate based upon hard outcomes -- just ask the 20oor folks -- its all about surrogate lipid markers and now Harry Potter's particle sizes. Did the insurance industry create the following of lipid panels was it marketing by pfizer and now AstraZ? Is it the NLA? or is it the guidelines committees? There are major academic medical centers trying hard to teach their residents & fellows to use Ev Based Med when available but the minute they leave the teaching environment they are pressured to use 1)what the insurance formulary will allow 2) what the latest speaker says to use 3) the path of least resistance (ie, whats in the sample closet)

Why else would there be 4 placebo controlled statin trials with "the most potent statin" conducted AFTER there had already been 3 studies conducted by the over-rated statin using active treatments as the control arm? Good question I think.

Industry Affiliated

July 12, 2010 09:47 (EDT)

you need to do your homework Michael

Costco will sell your patient 20mg of Zocor at less than 11 bucks for 100 tabs. That comes to below four bucks for a months supply.

Michael Cobble, M.D.

July 12, 2010 01:24 (EDT)

Thanks Evan

That was so nice and pleasant of you.

Yes, we did our homework. WalMart where many of our pts shop charges $25/mos, costco charges $10 for 90 days. I wasn't on here to advertise for commercial agencies but rather to point out that different pharmacies depending on geographic areas will charge different prices. it's good you did your homework, we do our homework to.

Michael Cobble, M.D.

July 12, 2010 03:13 (EDT)

Perhaps my post

Evan,

I rered my original post and perhaps it didn't explain the issue as it should.

We had a patient 2 weeks ago call and state the simvastatin I had written was too expensive, which shocked me. I had my nurse call the local pharmacies for prices on prava and simva which varied dramatically between $4-10/mos to as high as $25-65/mos. My point was that generic may not be the $4-10 30-100 day as we hope. Very frustrating to us all. Costco gave the best price, wal mart in our area not so great, others worse. This was 20-30 minutes of homework my nurse had other things she needed to do.

CJ McConnell

GB Pfizer rep,... possibly Lipitor ?

You really should know more about the drug you market [marketed ?].

Michael Cobble, M.D.

July 12, 2010 10:47 (EDT)

Atorvastatin beats rosuvastatin for kidneys | theheart.org

http://www.theheart.org/article/1095269.do
Industry

I think AZ supported this study at great risk. Very unusual population with dramatic macroalbumin 1000 mg (very high). These are very hard to find even the renal and DM clinics in our area would say finding 3-4 of these people is hard. The final publication will be interesting. The Adverse events were similar, we are uncertain in clinical practice what a drop from GFR of 80 to 74 in 60 year olds would mean. (I’m glad to see any GFR over 50 in this DM age group population) Each statin is uniquely metabolized and cleared, each statin now has evidence to support their use (efficacy, safety and outcomes in different settings). Has atorva shown benefit in Aortic stenosis or heart failure? Statins in end stage renal disease have been difficult at best as are most medications at that time. DV practices EBM and when faced with bad kidney function, he finds it best to use a hepatically cleared statin as do we. Rosuva has labeled from the beginning with FDA in poor renal clearance max dose is 10 mg and it would appear this also applies for people with UMA of 1000 mg (dramatic macroA). It would be interesting to see if a 5 year outcome study would show risk or benefit. Would the onus be on NIH or fed govt or industry to support head to head outcomes? People in medicine tend to be quite skeptical and cynical, however I have found the majority in clinical practice to have high integrity. Everyone has bias, I find many of my rx decisions are actually dictated by ‘mis’managed care, not the samples in closet or latest ‘speaker’ or rep lunch, etc. etc. all the best.

# 27 of 30 July 13, 2010 01:05 (EDT)

Melissa Walton-Shirley

Sorry gentlemen, I've been on vacation....and stil am but felt compelled to wade in a bit. Glen, you did exactly as asked and identified yourself. As long as you state your bias, all’s fair ...however, I don't think Mike is any kind of an industry rep. I think he's just stating his experience right Mike? DD....to say that Bradly Bale is over rated is terribly unfair. I find him exceptionally dedicated and excited about prevention...a lesson our entire medical system the world over really needs to learn.

Melissa

# 28 of 30 July 13, 2010 01:16 (EDT)

Michael Cobble, M.D.

I think GB was responding to CJ's comment. I like seeing both sides and feel they are nicely balanced. Yes when I saw the comment about Brad ‘an overrated FP’ my first thought was I don't think I've ever met an ‘overrated and some people might say appreciated FP’ have met a lot of overrated specialists and researchers, but uncertain I have ever met an overrated F.P. I held my tongue and have just giggled about that comment for the last week. F.P’s from my experience are uniquely underrated as are many in primary care.

# 29 of 30 July 13, 2010 09:44 (EDT)

Melissa Walton-Shirley

Mike

I would never over rate or under rate you. I think you are like porridge....just right :) Melissa

# 30 of 30 July 13, 2010 10:19 (EDT)

Michael Cobble, M.D.

Thanks Sometimes I feel like porridge at the end of clinical days. Can't say my schedule is as hectic as yours....... We both have jobs that don't respect our time much. End of day caring for the patient and getting that occasional thank you after listening to chief complaints all day is worth it.

Post a new comment

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