Trends-in-Medicine

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By Lynne Peterson

SUMMARY

Edema may not be a serious problem with CCBs, but it is bothersome, and that should make **Forest Laboratories' lercanidipine** a winner since edema is significantly less with lercanidipine than with Pfizer's Norvasc. There's no excitement about **Forest's Benicar**, and doctors see it primarily as a me-too drug in a crowded ARB market. There also is no enthusiasm for either **Pharmacia's Covera HS** or **Biovail's Cardizem XL**. Doctors either consider chronotherapy a gimmick, or they already are prescribing other antihypertensive medications at bedtime and see no need for these agents. **Pharmacia's eplerenone** is expected to appeal mostly to heart failure patients, diabetics and African-Americans. Half the doctors questioned are very concerned about the hyper-kalemia side effect with eplerenone. A cheaper, generic lisinopril is likely to appeal to managed care, but **King's Altace** is predicted to gain further market share.

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This meeting covered a range of topics, but, with the increased emphasis on lower blood pressure goals, this report focuses on a variety of medications to treat hypertension, including new calcium channel blockers, angiotensin II receptor blockers, aldosterone blockers as well as a new blood test to help gauge which medications should be given to which hypertensive patients. In addition to lectures, doctors attending the meeting were interviewed about the outlook for some of these medications.

CALCIUM CHANNEL BLOCKERS (CCBS): Forest Laboratories' Lercanidipine

Forest researchers and officials were emphasizing the value and importance of lercanidipine, a dihydro-pyridine (DHP) calcium channel blocker which it licensed from Recordati, in combination or second line therapy. On lercanidipine specifically, speakers said:

- It is as effective as losartan (Merck's Cozaar) in reducing system and diastolic blood pressure in diabetic hypertensives.
- One year of lercanidipine treatment induces a greater reduction in LVMI than losartan, independent of blood pressure reduction.

Forest officials made it clear that the big marketing claim with lercanidipine will be a lower incidence of edema – and, therefore, a lower discontinuation rate – compared to other CCBs. The relative risk of discontinuation of antihypertensive therapy over six years is: .99 with diuretics, .77 with ACE inhibitors, .71 with alpha blockers, and .56 with CCBs. A speaker said, "Edema is clearly dose-dependent and an issue with nifedipine; 10 mg of amlodipine is associated with a 40% incidence of edema, and 20 mg with a >80% incidence of edema. In the COHORT trial, lercanidipine…showed less edema…but efficacy was comparable." COHORT was a randomized, double-blind study of hypertensive patients age ≥60 for a minimum of six months and up to 24 months.

COHORT Results

Measurement	Lercanidipine 10-20 mg n=420	Amlodipine 5-10 mg n=200	Lacidipine 2-4 mg n=208
Edema	8.3%	18.5%	4.3%
Total drop-outs for edema	2.1%	8.5%	1.4%
Dropouts for edema at ≤ 6 months	1.9%	7.5%	1.0%

In clinical practice, edema is an issue with Pfizer's Norvasc (amlodipine), but it is more of a nuisance than a serious problem. A New York doctor said, "Edema is not a big issue or Norvasc wouldn't be such a big seller." A New Hampshire doctor said, "Edema is an issue with Norvasc, but it doesn't have much impact on my use because most patients are on dual therapy – Norvasc plus an ACE inhibitor

– and that resolves it. CCBs shouldn't be monotherapy." A North Carolina doctor said, "Edema is a problem, not huge but a bother." Another doctor said, "Edema is very prevalent, and I think it is a real issue." A New York doctor estimated, "Thirty percent of my Norvasc patients get edema." A New Mexico doctor said, "Edema is very significant with Norvasc. Eighty percent of my patients note it – but GI problems are a worse issue."

Doctors predicted that lercanidipine will do very well competing with Norvasc. One expert said, "Certainly, they will play off each other. The absolute best CV seller is Norvasc. That is a very powerful, smooth acting CCB. It's a no-brainer concept drug. You can give it to the elderly, the young, women, blacks, etc., and to patients with all kinds of co-morbidities -- and it works. The only drawback is ankle edema with monotherapy. Most women taking it are concerned about the edema, despite their physician's assurance that it is not serious. So, now, if there is a drug with half the incidence of edema, like lercanidipine, it has a distinct advantage. I think physicians will switch." A New York doctor said, "I believe in it. In theory, it makes sense." A New Mexico doctor said, "Lercanidipine will do great if the edema is really lower than Norvasc, and the price is the same or lower." Another doctor said, "If it is cheaper or a patient has real edema, I may try it."

Lercanidipine is likely to be used mostly for new patients, but patients who complain of edema also may be switched to it. A doctor said, "I will use it for older females and diabetics, and I'll switch patients who complain of edema on Norvasc." A New York doctor said, "I'll use it for new patients and I'll switch some patients, especially diabetics and glitazone users." A New Mexico doctor said, "I'll use it for new patients and when patients on another drug need a dosage change, but otherwise I won't switch patients from another drug."

However, U.S. doctors are not entirely convinced about the lercanidipine edema data because it is from a European trial. They would like to see a U.S. trial confirming a lower rate of edema with lercanidipine. A North Carolina doctor said, "I'm very skeptical. I don't tend to switch patients because some new drug makes claims that don't pan out – and it takes a lot of time to change a patient's medication."

Novartis has its own plan to countermarket against lercanidipine – combination therapy. Only about 30% of hypertension patients are on monotherapy today, and adding an ACE inhibitor to Norvasc counteracts the edema. Novartis has introduced Lotrel (amlodipine +benazepril), a combination ACE and CCB. Lotrel is priced lower than high-dose (10 mg) Norvasc. An expert argued that lercanidipine is better for monotherapy patients than Norvasc, and Lotrel is better for the combination therapy patient. He said, "There is no head-to-head data on lercanidipine and Lotrel, but with Lotrel, the edema disappears in 70%-80% of patients. In contrast, lercanidipine has around a 50% disappearance rate. So, if the question is edema only, then a doctor may want to consider using lercanidipine because you aren't introducing an additional chemical compound. For patients who need combination therapy, Lotrel is best, and patients do prefer taking one pill to two, but combination therapy just to treat edema may be too much."

Polypharma (combination therapy) has become the norm in treating hypertension. Among the more general points speakers made about CCBs were:

- "Patients with both diabetes and hypertension are at greatest risk of developing ESRD and before that many of them have CRI, and there is an opportunity to intervene there."
- "Even in people with acceptable blood pressure control BP, aggressive blood pressure therapy reduces progression to albuminuria."
- "CCBs are safe and effective and may be superior to diuretics and beta blockers." There was a concern in the mid-1990s that CCBs might increase MI rates, and this slowed down the use of these drugs in the U.S., but speakers insisted that numerous trials have shown that this concern was misplaced.
- "Most studies have shown that CCBs are worse in terms of MI than conventional therapy, but better in terms of stroke, but the NORDIL study found the reverse."
- "CCBs are appropriate first-line therapy for hypertension."

SELECTIVE ALDOSTERONE BLOCKER (SAB): Pharmacia's eplerenone

Doctors did not appear very excited about eplerenone. They expect it to be used mostly for heart failure, with the outlook weak in hypertension, except for diabetics, African-Americans, and perhaps some other subgroups.

A key reason for this outlook is concern over the hyperkalemia side effect (potassium elevation). In the 4E LVH study, presented at the American College of Cardiology in March 2002 , potassium ≥6.0 mmol/L occurred in 10.9% of eplerenone (200 mg) patients, compared to 2.8% of enalapril (40 mg) patients and 4.5% of patients on a combination of eplerenone 200 mg and enalapril 10 mg.

Half the doctors questioned about hyperkalemia with eplerenone insisted it is a serious problem. A New Mexico doctor said, "It is a real issue, especially in patients with early kidney disease." A North Carolina doctor said, "It is very much a concern. The average doctor is very frightened by hyperkalemia." Another doctor said, "It's a real issue and a possible problem." A New York doctor said, "There's been a lot of noise about this, but all spironolactones will cause hyperkalemia in patients pre-disposed to it. But also, a lot of these patients are taking homeopathic remedies and over-the-counter mediations that contain a lot of potassium."

The other half of the doctors questions dismissed the hyperkalemia as clinically unimportant. One said, "There is no concern if the patient has normal kidney function. I think that will require physician education, but that is do-able." A New Hampshire doctor said, "It's really not an issue. I'm not worried about it. You just have to monitor patients." A Louisiana doctor said, "Eplerenone is exactly what I'm looking for in severe hypertension. Eplerenone will scavenge all the difficult-to-treat anti-hypertensives. It will cannibalize spironolactone. But I probably would not put uncomplicated patients on it as step one. I would use it for a patient who is a candidate for strokes, and lercanidipine+eplerenone would be a good combination. In hypertensive patients with CHF, I would lean to Lotrel because Norvasc has been shown safe there."

Most doctors – including many of those who are not worried about hyperkalemia – predicted that eplerenone may have a more limited role and/or a slower launch than the company probably wants. A North Carolina doctor said, "The company is making a big push for this drug, but it can't launch it until the hyperkalemia issue is resolved." A New York doctor said, "I think eplerenone will have a tough time in the hypertension market. It's place will be in CHF." A New Mexico doctor said, "The outlook is questionable right now."

The 6,200-patient EPHESUS (Eplerenone Post-AMI Heart Failure Efficacy and Survival Study) mortality and morbidity study will determine whether eplerenone has a beneficial effect on survival and morbidity in patients with AMI complicated by heart failure due to systolic LV dysfunction. This is combination therapy, with 25-50 mg qd eplerenone given on top of existing therapy. This trial also should clarify the hyperkalemia issue. Enrollment ended in December 2001, and there have been about 150 events so far. Results are expected at the American College of Cardiology in 2003.

At a symposium on eplerenone, sponsored by Bristol, speakers said:

- The animal data on eplerenone is strong.
- Proteinuria and nephrosclerosis are reduced with aldosterones.
- Aldosterone is a mediator of progressive renal disease -- independent of the renin-angiotensin system.
- A 75 mg dose of spironolactone is equivalent, in most situations, to 100 mg of eplerenone.
- Aldosterones are efficacious. A speaker said, "It is becoming increasingly clear that aldosterone, in addition to an ACE inhibitor, potentiates the effects."
- Eplerenone appears to provide end-organ protection.
- Aldosterone-induced cardiovascular injury involves all target organs, with inflammation possibly a major mechanism that can only be prevented by receptor blockade.

Eplerenone Results

Results at 16 weeks (final visit)	Placebo	Eplerenone 50-100-200 mg	Losartan 50-100 mg
Change from baseline SBP			
Blacks	-3.7	-13.5	-5.3
Whites	-3.2	-12.3	-8.5
Change from baseline SBP			
Blacks	-4.8	-10.2	-6.0
Whites	-6.4	-11.1	-8.4

CHRONOTHERAPY: Pharmacia's Covera HS and Biovail's Cardizem XL

Phase III data on Cardizem XL (diltiazem) was positive, but the results of Pharmacia's CONVINCE trial of Covera HS (verapamil) were disappointing. CONVINCE tested Covera HS against atenolol in 16,400 patients and missed its primary endpoint of proving equivalence in preventing outcomes. Biovail had hoped to use CONVINCE to support use of its drug by proving the concept of chronotherapy.

These results did not surprise doctors at the meeting; most already were less then enthusiastic about either drug. A new Hampshire doctor said, "I'm not convinced about Cardizem XL. I'm not sure chronotherapy is clinically relevant, and cost is an issue." A Pennsylvania doctor said, "Chronotherapy is a marketing gimmick. I'd need more than one (positive) study to be convinced." Another source said, "The companies' claims are probably true, but I already give other medications at night." A New York doctor said, "They are not a gimmick, but why do we need them? Do you change the blood pressure form a dipper to a non-dipper, and does that cause more harm than good?"

ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs): Forest's Benicar

There was absolutely no interest in or excitement about Benicar (olmesartan medoxomil), with doctors describing it as a me-too drug in a crowded ARB market. Unless managed care forces its use, uptake is expected to be very slow, sources predicted. One doctor said, "It will be hard to sell this drug." Another said, "It may be better than what we have, but it will be hard to sell a new ARB." A third said, "I won't use it. There's no advantage to it (over other ARBs)."

At a Forest/Sankyo-sponsored symposium, speakers emphasized the advantages of ARBs over ACEs, with particular emphasis on the safety of ARBs. One said, "There is a traditional trade-off between dose-related efficacy and adverse

events. With most agents, the adverse event profile tracks efficacy, but at a slightly lower rate. With ARBs, there are no more side effects than with placebo." A Forest official predicted that, at least initially, Benicar, a prodrug, would be prescribed primarily for new patients and as doctors gained more experience with it, some switching form other agents might occur.

Speakers emphasized that the efficacy of ARBs in general, not only for their blood pressure lowering effects but also for reducing cardiovascular mortality, stroke and new-onset diabetes. Speakers suggested that ARBs (including Benicar):

- Prevent narrowing of arteries.
- Prevent progressive nephropathy in Type 2 diabetes. One speaker said, "The use of ARBS in Type 2 diabetes is associated with renal protection. "The animal data for olmesartan (Benicar) looks similar and is probably stronger than the other sartans….Using rats, you can show that it reduces proteinuria." Another speaker said that the data is not clear yet whether ACE inhibitors are renal-protective.
- Slow or prevent diabetic neuropathy.
- Do not have as great an effect on bradykinin as ACE inhibitors, but a speaker suggested that was not important, "I don't know what that means, but the bradykinin effect may not be as important in humans as in rats."
- Improve endothelin function faster than ACE inhibitors, within a year.
- Have a stroke-lowering benefit.

ACE inhibitors and ARBs are probably identical in terms of hyperkalemia. A speaker said, "I believe that these patients should be on diuretics and not on strict sodium restriction because I think that is helping us in terms of seeing less hyperkalemia in this patient population…Where there is a risk of getting in trouble -- and we seeing cardiologists doing this -- is adding an ACE to an ARB and vice versa – and even adding spironolactone. And the problem may be even worse with the new aldosterone inhibitor (Pharmacia's eplerenone)."

Blood Pressure (n=326)	Benicar 20 mg qd	Atenolol
Seated diastolic BP	-14.0%	-14.3%
Seated systolic BP	-20.7%	-12%

Not all ACE inhibitors or ARBs are the same, experts insisted. A speaker said, "I think there are differences between the different ACEs and different ARBs, but they don't seem to be dramatic differences, though in blood pressure lowering there may be some differences. (There are) dramatic blood pressure lowering effects of olmesartan (Benicar). I don't think there is evidence of tissue-ACE having a dramatically different effect. I don't believe tissue-ACE exerts a significant effect on different ACE inhibitors. In ARBs, there are differences – some appear to be more potent than others and some have a longer duration of action."

Blood Pressure (n=440)	Benicar 20 mg qd	Amlodipine	Placebo
Seated diastolic BP	-10.6%	-9.7%	-3.6%
Seated systolic BP	-10.9%	-10.9%	-1.3%

Benicar was described as similar in efficacy to other ARBs -- but safer. One speaker said, "With the exception of dizziness, Benicar appears better than placebo in terms of side effects."

Blood Pressure (n=440)	Benicar 20 mg qd	Amlodipine	Placebo
Seated diastolic BP	-10.6%	-9.7%	-3.6%
Seated systolic BP	-10.9%	-10.9%	-1.3%

Some of the characteristics of Benicar are:

- Biovailability ~25%
- Extensively bound to albumin (>99%)
- No accumulation at steady-state
- Tmax ~2 hours
- Dual elimination -- 35-50% renal, 50-60% liver
- Long half-life, which is:
  - > Longer than candesartan, eprosartan, losartan and valsartan.
  - > Comparable to irbesartan
  - > Shorter than telmisartan

COMBINATION MEDICATIONS

Blood Pressure	Benicar 20 mg qd	Losartan 50 mg	Valsartan 80 mg	Irbesartan 150 mg
Seated diastolic BP	-11.5%	-8.2%	-7.9%	-9.9%
Mean 24-hour ambulatory diastolic BP	-8.5%	-6.2%	-5.65	-7.4%
Mean 24-hour ambulatory systolic BP	-12.5%	-9.0%	-8.1%	-11.3%

Some sources said there has been resistance by managed care to combination medications. A New Mexico doctor said, "We just about can't get any combination medications on formularies because then managed care doesn't get two co-pays."

Abbott's Tarka (trandolapril+verapamil). The Abbott sales reps were educating doctors about this agent, but it did not appear to be a major topic of lectures.

Novartis' Lotrel (a fixed combination of amlodipine and benazepril). Researchers reported on results from the 9,208-patient LOGIC study. In this four-week, open-label trial, 7,468 patients who failed to reach diastolic blood pressure of <90 mmHg with on amlodipine alone (at 5 or 10 mg) were

switched to Lotrel (5/10 or 5/20). After four weeks of treatment, Lotrel significantly lowered both systolic and diastolic pressure (an average of 15.6 and 11.5 mmHg, respectively).

Another group of 1,739 LOGIC patients who experienced pedal edema (swelling of the feet and ankles) also were switched from amlodipine to Lotrel. Pedal edema improved in 85% of these patients.

LOGIC Results

Measurement (n=45)	Group 1 (7,468 patients)	Group 2 (1,739 patients)
Reduction in mean sitting diastolic BP At 4 weeks	-11.5 mmHg	-11.1%
Reduction in mean sitting systolic BP at 4 weeks	-15.6 mmHg	-11.4%
Microalbuminuria	-24.6%	-19.7%

Results from several other, small Lotrel trials were presented, including an Italian study of 45 hypertensive patients with diabetes and microalbuminuria.

Italian Study of Lotrel

Measurement (n=45)	Lotrel (5 mg amlodipine+ 10 mg benazepril)	Benazepril 10 mg monotherapy
Systolic BP	-15.1%	-11.1%
Diastolic BP	-16.3%	-11.4%
Microalbuminuria	-24.6%	-19.7%

ACE Inhibitors

King Pharmaceuticals' Altace. Most sources predicted that generic lisinopril would not negatively impact Altace (ramipril) as much as other ACE inhibitors. However, they predicted generic lisinopril would have quick and huge uptake since managed care formularies often dictate which ACE inhibitor is used. A New England doctor said, "The impact of generic lisinopril will be huge, depending on its price. If the price is significantly less, lot of managed care patients will use it. All my quinapril (Pfizer's Accupril) patients will convert to it. But ramipril shouldn't see any loss; it is still strong." A Pennsylvania doctor said, "Patients are more and more concerned with cost, so we are paying more attention to generics."

Many doctors believe in the "tissue-ACE" effect, and that, along with the HOPE trial data, has been helping Altace use. Thus, most sources predicted that Altace will continue to grow its market share somewhat for the near future. One said, "Ramipril still has legs, and I understand the company is going to lower the price." A New York doctor said, "I would never use generic lisinopril because it is not a tissue-ACE. Managed care will continue to have ACE brand on formulary." A New Mexico doctor said, "Ramipril will keep increasing market share for a while, but then it will plateau. Generic lisinopril will hurt ramipril because of formularies."

Abbot/Knoll's Mavik (trandolapril). This is the only ACE inhibitor with a specific indication for blacks and patients with low-renin levels, and Abbott sales reps were emphasizing those points. Abbott sales also expect to start selling **Tricor** (fenofibrate) in about eight months, and the claims are expected to be that it raises HDL and lowers triglycerides.

Renin Testing

Nichols Institute Diagnostics, a division of Quest Diagnostics, has developed a test that can determine the type of hypertension patients have, and a prominent speaker suggested that this is the way medications will be chosen in the future. He said, "I think the DHP-CCBs are good and give better flow, but that comes at a cost…The way of the future is to find out what kind of hypertension a patient has – sodium volume hypertension or renin-hypertension – and prescribe therapy accordingly. There is a big place for drugs like lercanidipine, which has modest advantages over its predecessors...We don't' need to give every patient the same regimen. We need to sort out at the beginning whether you have a CCB or an ARB patient…Combination therapy is a key advance, but every patient should get the correct drug for his or her hypertension. Now have new renin test that…can sort out whether the hypertension is due to renin or sodium.

An expert has devised a protocol for how to use this test

	First Visit Blood test	
	‖	
	Second Visit	
30% of patients DR<5 **sodium volume HT** Start a diuretic		70% of patients DR>5 **renin-mediated HT** Start a beta blocker
	Third Visit 25% of patients controlled	
If not controlled, increase diuretic, ARB or CCB (not ACE)		If not controlled, increase beta blocker, ACE or ARB (not diuretic or CCB)
	Fourth Visit 50% of patients controlled	
If not controlled, add beta blocker		If not controlled, add diuretic
	Fifth Visit 75% of patients controlled	
If not controlled, increase beta blocker		If not controlled, increase diuretic
	Sixth Visit 90% of patients controlled	
If not controlled, stop beta blocker and add second diuretic		If not controlled, stop diuretic

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