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INSIDE

Special Report: Back to Betas

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Special Report: Back to Betas

Beta blockers rediscovered, gain primary role in cardiology

Cohorts, consortia calling for increased use in CHF, post-MI therapy

Hospital pharmacists and pharmacy and therapeutics teams need to reassess their institutions' protocols for the use of beta blockers in the treatment of congestive heart failure (CHF) and post-myocardial infarction (MI) therapy, research shows.

The traditional beta is being roundly touted for its ability to curb morbidity and hospitalization in these patients, with current research decrying the underuse of beta blockers as much as it champions the drug's benefits.

The case for beta blockers has been growing in recent years, with large-scale trials and cohorts given consistent high-profile space in major medical journals since 1997. Last November, the American Heart Association called on physicians to increase the use of beta blockers in post-MI therapy during the organization's 69th scientific sessions in New Orleans. The American Medical Association also has noted its support for greater use of beta blockers.

This year, a consensus group of 150 heart failure researchers and cardiologists, working as the Advisory Council to Improve Outcomes Nationwide in Heart Failure (ACTION HF), strongly stressed the need for the inclusion of beta blockers in the treatment of CHF. The consortium recommends a four-drug regimen of traditional diuretics and digitalis, along with the combination of ACE inhibitors and beta blockers.

Live-saving potential

"We know that treatment with a four-drug combination is the optimal treatment for most patients with heart failure, and utilization of this strategy can dramatically affect the outlook for patients," says **Milton Packer**, MD, co-chair of ACTION HF and director of the Center for Heart Failure Research at New York Presbyterian Hospital. "If we could get every eligible heart failure patient to receive an ACE inhibitor and a beta blocker, we could prevent hundreds of thousands of hospitalizations and save tens of

thousands of lives," he said in a written statement.

The recommendations follow 18 months of research by the group, which charged itself with reviewing every available study and cohort on CHF treatment. The group also stresses that only about 40% of eligible patients receive ACE inhibitors, while just 5% receive beta blockers.

Researchers and pharmacists say the reason for that is twofold, based on early concerns that beta blockers, by lowering the heart rate, would produce exactly the opposite effect desired. They also say other drugs, primarily calcium channel-blockers (CCBs), simply became more popular.

"I think the science just caught up with the reality," says **Barry Browne**, PharmD, coordinator of Drug Information Services at Scott & White Hospital in Temple, TX. "It had been the conventional wisdom in the mid to late '80s not to use beta blockers for CHF because of the resting effect. For post-MI, the idea is to give the heart a chance to rest with a beta blocker, and again the thought was betas should not be used for CHF simply because resting is bad," he says.

Benefits outweigh risks

The science Browne refers to centers on new information about the mechanism of heart failure; betas are thought to block the adverse action of certain hormones released when the heart is damaged. In other words, blocking of adrenaline receptors and the effects of those chemicals outweighs any slowing of the heart rate that beta blockers are known to cause as traditional hypertensive drugs. ACE inhibitors also work by blocking the release of "stress" hormones.

The assertion that beta blockers were squeezed out of the market by calcium channel-blockers is backed by a 1998 study at Massachusetts General Hospital. That study noted that despite existing guidelines calling for beta blocker use, prescriptions declined in the '80s as the use of CCBs rose. The study even followed drug advertisements in 210 issues of the *New England Journal of Medicine,* which found that in 1985, 12% of ad space dealt with beta blockers, and 5% advertised CCBs. By 1996, 27% of the ads were for CCBs, while no ads appeared for beta blockers the entire year.

If the case is being made for an increased use of, and a return to, beta blockers, then formulary considerations can't be far behind for both CHF and post-MI therapy.

Coreg as a formulary consideration

For CHF therapy, the biggest formulary consideration facing pharmacy and therapeutics committees is SmithKline Beecham's Coreg (carvedilol), the first beta blocker approved for CHF. The drug offers beta-blocking and vasodilating effects, and like all beta blockers, it offers improved left-ventricular function by blocking excessive adrenergic stimulation. Carvedilol also shows no effect on cholesterol levels in trials.

The drug is specifically indicated for mild or moderate CHF, used in conjunction with digitalis, diuretics, and ACE inhibitors in heart failure of ischemic or cardiomyopathic origin due to left-ventricular systolic dysfunction. SmithKline Beecham recommends starting patients on the lowest possible dose, if the patient can tolerate it. Specifically, the company recommends a starting dose of 3.125 mg twice daily for two weeks, followed by an increase to 6.25 mg, then doubled every two weeks until tolerance is capped.

Side effects to watch for include dizziness, bradycardia, hypotension, or signs of worsening heart failure. Contraindications include patients with bronchial asthma. The drug is available in 3.125 mg, 6.25 mg, 12.5 mg, and 25 mg strengths in 100-tablet bottles at $154 a bottle.

For hospital pharmacists such as Browne at Scott & White, there are several formulary

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considerations to weigh. "Coreg needs to be monitored on the dose change, and there is the problem of finding the time to monitor patients in a primary care setting. You need someone who will watch patients very closely," says Browne.

"The drug is not a cure, so the question is, do you add it to your formulary knowing there is a limit and that there is monitoring? You don't want to put all of your patients on Coreg. In mild cases it may not be needed, and in severe cases it may not help, so the best benefits would be for select patients," he says.

Beta studies in detail

More clinical information is expected from a large post-market study begun by SmithKline Beecham aimed at enrolling 6,000 CHF patients in a yearlong tracking surveillance program. The company hopes to publish the results in 2000.

The evidence that's been mounting the case for beta blockers in CHF and post-MI treatment has peaked during the last three years, with early 1999 reports coinciding with coordinated announcements like that from the Advisory Council to Improve Outcomes Nationwide in Heart Failure.

In January, for example, the American Heart Association detailed the results of a study in which death rates were nearly halved among 2,647 patients with mild or moderate heart failure who were given beta blockers. Patients received either diuretics and ACE inhibitors or the two drugs and the beta blocker bisoprolol. All of the patients in the study had been diagnosed with left-ventricular systolic dysfunction leading to stable, symptomatic heart failure.

Doses started at 1.25 mg per day, increasing to 10 mg per day over six months. Patients in the beta blocker group had 34% fewer deaths from all causes and 44% fewer sudden deaths.

"The trial is an important turning point," says the hospital association's **Harlan Krumholz**, MD. "Small studies have been accumulating, suggesting the value of beta blockers for patients with heart failure, but this trial provides the first real convincing evidence that patients with mild or moderate heart failure live longer and have less need for hospitalization when treated with beta blockers." Krumholz, an associate professor of medicine at Yale University, points out, however, that the study was inconclusive concerning patients with severe heart failure. "We need more information about these [patient] groups."

Some of the earlier studies Krumholz refers to also pertain to beta blockers in post-MI therapy. One such study followed the use and outcomes of beta blocker therapy in 1,165 patients following cases of acute MI treated within a Kaiser HMO plan in northern California.

The study basically found that beta blockers were being underprescribed, despite being "beneficial in patients after an acute myocardial infarction," in part due to concern over the relatively large dosages physicians thought were needed. That led to fewer and lower doses being prescribed than have been found to be effective in clinical trials. But the study found that smaller doses worked just as well in terms of patient mortality. (For details, see *Arch Intern Med* 1998; 158:449-53.)

As to the results of the study, researchers wrote, "Of the 37.7% of patients prescribed beta blocker therapy, 48.1% were treated with dosages less than 50% of the dosage found to be effective in preventing cardiac death in large randomized clinical trials. Compared with patients not receiving beta blockers, those treated with lower-dosage therapy appeared to have a greater reduction in cardiovascular mortality than patients treated with a higher dosage."

Some patients get CCB instead

A similar study pointed out that among patients 65 or older with no contraindications to beta blockers, only 50% were getting prescriptions, and those patients receiving CCBs were even less likely to be given a beta blocker. The national cohort study examined more than 100,000 patients, finding that of the 45,308 clearly eligible for beta blockers, only half were receiving them. (For details, see *JAMA* 1998; 280:623-629.) The study also found that the patients who did receive beta blockers had a 14% lower risk of mortality at one year after discharge.

A year earlier, Harvard researchers made the same point in a cohort of post-acute MI Medicare patients in New Jersey. (See *JAMA* 1997; 277:115-121.) In that study, of the 3,737 patients over age 65 deemed eligible for beta blockers, 785 received them; the majority received CCBs instead.

The Harvard researchers concluded that "those patients who did receive beta blocker therapy following acute MI were 43% less likely to die within two years than patients who received calcium channel blockers and about 22% less likely to be rehospitalized. Yet, as a whole, elderly patients were three times more likely to receive a new prescription for costlier calcium channel blockers than for beta blockers." ■

Betas find another cardiology role

Combo with digoxin favorable in AF treatment

For patients with chronic atrial fibrillation (AF), combining the beta blocker atenolol with digoxin therapy led to the best heart rate control, according to a February study of five regimens conducted at a California Veterans Administration Medical Center. (The American College of Cardiology is publishing the findings. **See box, above right for contact information.**)

Like its historical use in treating congestive heart failure, digoxin has long been a first-line monotherapy for AF treatment.

But according to research led by **Bramah Singh**, MD, of the VA Medical Center of West Los Angeles, the most effective treatment combines digoxin and a beta blocker. To reach that conclusion, Singh and colleagues compared five regimens divided among 12 patients with chronic AF. The regimens included patients receiving digoxin; the calcium channel blocker diltiazem; the beta blocker atenolol; a combination of digoxin and diltiazem; or a combination of digoxin and atenolol.

The use of all three drugs as separate monotherapies did result in decreased heart rate and control, with digoxin surprisingly performing least effectively by itself, according to Singh. What's more, as a monotherapy, the beta blocker outperformed the other drugs, he adds. But overall, and based on effective control over a 24-hour period, the beta-digoxin combination performed the best.

"Although digoxin has been very widely used, it is not very good at controlling the heart rate, especially during activities of daily living," says Singh. "The best control we achieved with a single drug was with the beta blocker, but when we combined it with digoxin, we achieved almost ideal control of the heart rate."

Singh says the way the two drugs work separately is the key to success. "Digoxin favorably modulates the parasympathetic nervous system, while atenolol blocks the effect of the sympathetic nervous system, which drives the heart rate. Together, the two drugs achieve a synergistic effect in which the total of their combined effects is greater than the sum of their individual effects." ■

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- **SmithKline Beecham** (Coreg), 200 N. 16th St., Center City, Philadelphia, PA 19101. Phone: (800) 366-8900.
- **American Heart Association**, 7272 Greenville Ave., Dallas, TX 75231. Phone: (800) 242-8721.
- **American College of Cardiology**, 9111 Old Georgetown Road, Bethesda, MD 20814. Phone: (800) 253-4636.
- **Bramah Singh**, MD, VA Medical Center of West Los Angeles, 11301 Wilshire Blvd., West Los Angeles, CA 90073. Phone: (310) 268-3646.

Genetic drug on tap for acute CHF

FDA committee OKs hormone-derived treatment

In January, the Food and Drug Administration's cardiovascular and renal drugs advisory committee recommended the first genetically engineered drug therapy for chronic heart failure (CHF) treatment. Scios Inc. in Mountain View, CA, is seeking an indication for Natrecor (nesiritide) as a short-term treatment for acute episodes of CHF.

The drug is the genetically engineered form of the cardiac hormone b-type natriuretic peptide

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(hBNP), which the body secretes in response to its failing heart. The company filed its new drug application in the spring of 1998 after Phase III trials. Trial outcomes included decreases in pulmonary capillary wedge pressure, a distinct blood pressure marker of the heart that researchers know can force fluid into the lungs if not controlled; and increases in the amount of blood pumped into circulation for the internal organs, known as the cardiac index.

Bayer AG has entered into an agreement to market the drug upon final approval. (For more on nesiritide, consult Scios' Web site at www.sciosinc.com.) ■

States seeking pharmacist reimbursement system

NABP, Mississippi model expanding

Five states are entering contracts with the National Association of Boards of Pharmacy (NABP) in Park Ridge, IL, to establish pharmacist credentialing tests for disease state management reimbursement, based on the Medicaid plan established last summer in Mississippi.

Ohio, Louisiana, Alabama, Rhode Island, and Oklahoma are seeking to offer pharmacist exams in diabetes, asthma, anticoagulation, and dyslipidemia clinical pharmacy, in anticipation of setting up a pharmacist reimbursement system for those services that is similar to the Mississippi plan.

Credentialing and reimbursement bloomed last summer when the Health Care Financing Administration approved a plan by Mississippi's Medicaid program and state pharmacy board to begin paying pharmacists for clinical disease management in the four disease state areas, provided a credentialing process was in place.

To get that done, the Mississippi board turned to the NABP, the National Association of Chain Drug Stores, and the National Community Pharmacists Association. The three groups merged as the National Institute for Standards in Pharmacist Credentialing (NISPC) and began establishing credentialing standards.

Soon after, though, organizations like the American Pharmaceutical Association (APhA) and American Society of Health-System Pharmacists (ASHP), for example, balked at the idea that just three organizations could or should set the standards. But based on a two-day conference on the issue last September that was hosted by seven national pharmacy organizations not a part of the new NISPC, a consensus plan has been reached allowing input by various organizations into the credentialing process under the NABP umbrella.

The meeting was hosted by APhA, ASHP, the American Association of Colleges of Pharmacy, American College of Apothecaries, American College of Clinical Pharmacy, American Society of Consultant Pharmacists, and the National Council of State Pharmacy Association Executives.

The process has opened the door for more state pharmacy boards to set up testing and approach individual state Medicaid programs on the possibility of reimbursement. "The interest level and support among individual pharmacists is quite high. Several pharmacy schools have also said they support what we're doing and asked how they can assist and work with their state boards," says **Carmen Catizone**, NABP executive director.

Adds Alabama pharmacy board secretary **Jerry Moore**, "We hope we can convince the third parties that this is a good way to do it. It's a mechanism by which the pharmacy board can protect the public health and practitioners can get reimbursed for their cognitive services."

In another expanding area of clinical pharmacy, that of specialty certification, the national Board of Pharmaceutical Specialties (BPS) in Washington, DC, added 367 pharmacists to its certification rolls based on 1998 test results, buoyed by its first offering of certification testing in oncology pharmacy.

Specifically, 118 of 207 pharmacist candidates passed oncology certification tests. In the four other specialties BPS offers, 32 pharmacists became credentialed in nuclear pharmacy, bringing the total number of certifications to 431; 14 passed nutrition support pharmacy tests for a total of 506 pharmacists certified; 166 passed

For More Information

- ❏ For more on Medicaid reimbursement plans, contact the **National Association of Boards of Pharmacy**, 700 Busse Hwy., Park Ridge, IL 60068. Phone: (847) 698-6227. Also, see October 1998 and January 1999 ***Drug Utilization Review***.
- ❏ For more on BPS testing and eligibility requirements, contact the **Board of Pharmaceutical Specialties**, 2215 Constitution Ave., Washington, DC 20037. Phone: (202) 429-7591.

pharmacotherapy, bringing that number to 1,413 certified; and 37 more pharmacists became certified in psychiatric pharmacy, bringing the total to 265 pharmacists certified in psychiatry since testing began in 1992.

The board began offering nuclear pharmacy certification in 1978 and nutrition support and pharmacotherapy certifications in 1988. ■

PBM satisfaction up slightly, survey shows

Employers, HMOs weigh in for annual survey

Pharmacy benefit managers (PBMs) score higher marks in their performance of administrative and operational functions than in their ability to produce utilization management, according to the Pharmacy Benefit Management Institute's (PBMI) annual survey of the employers and HMOs who use PBMs nationwide.

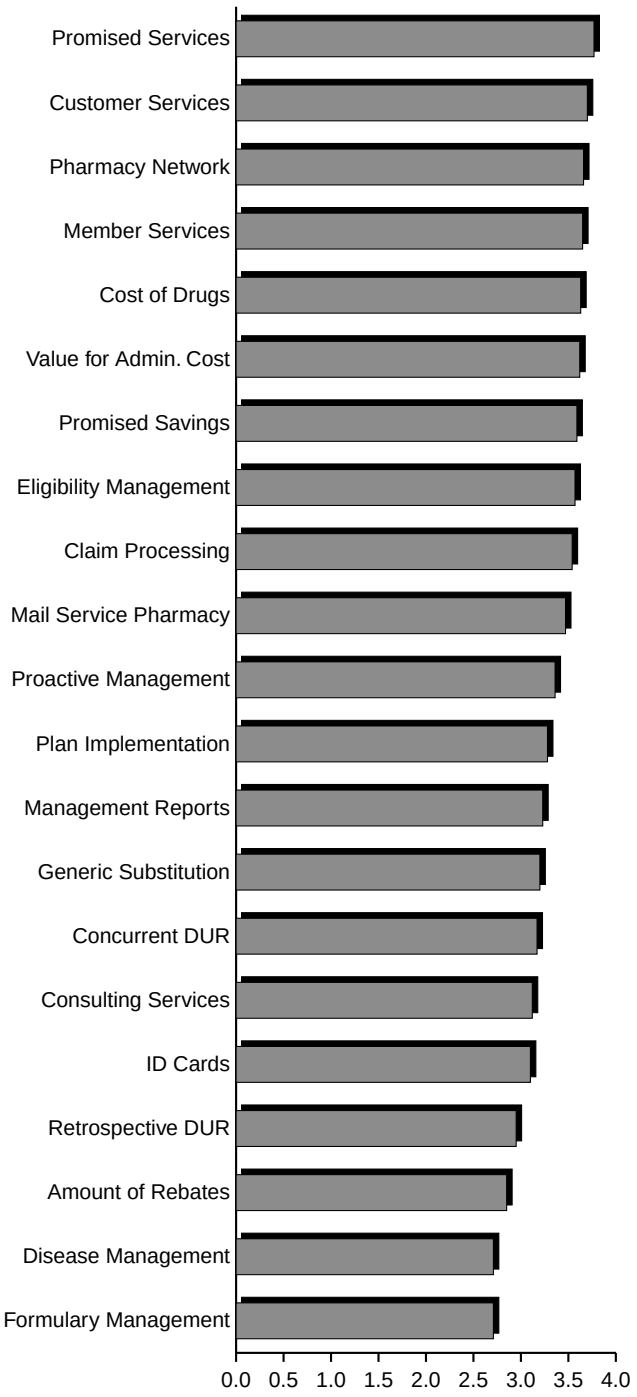
For the 1998 survey, responses were compiled from representatives of 330 employers, each with an employee population of more than 2,500 enrolled in health plans, and from 69 HMOs encompassing some 10 million enrolled. Each was asked to rate 22 PBM services from a low to high performance scale of 1 to 10, then place a separate score of 1 to 4 on the importance of the same services. **(See charts, at right and on pp. 63-64.)**

The average performance scores were similar among both groups, with pharmacy network management topping both scales and disease management fairing poorest with both groups. But at the same time, both groups placed the highest and lowest importance on those same categories. Neither group was happy with the cost of drugs or the reality of promised savings, aspects both ranked high in their importance scores.

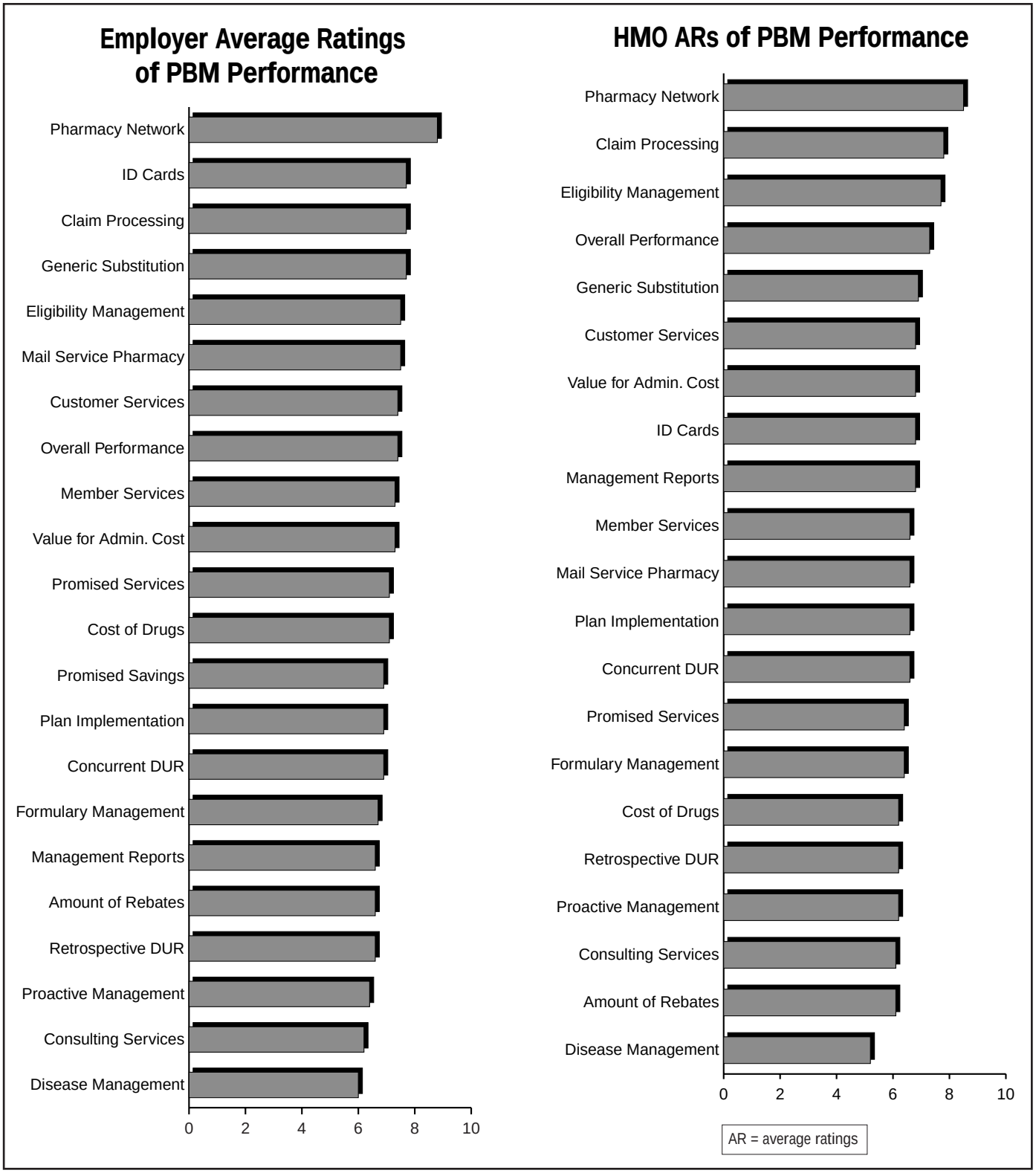
Formulary management also rated poorly, averaging a 6.7 score among employers and a 6.4 among HMOs, while both groups also placed formulary management among the lowest in terms of importance. Putting all scores together, employer satisfaction increased from a 7 to a 7.4 score compared to last year's survey, with HMO satisfaction rising overall from 6.2 to 7.3.

Within the overall dissatisfaction with drug utilization management, both employer and HMO representatives focused their concerns on inadequate management reports, failure to identify opportunities for utilization management, and failure to act on those opportunities when they are identified.

In perhaps the most telling information included in the follow-up conversations between institute surveyors and respondents, "many



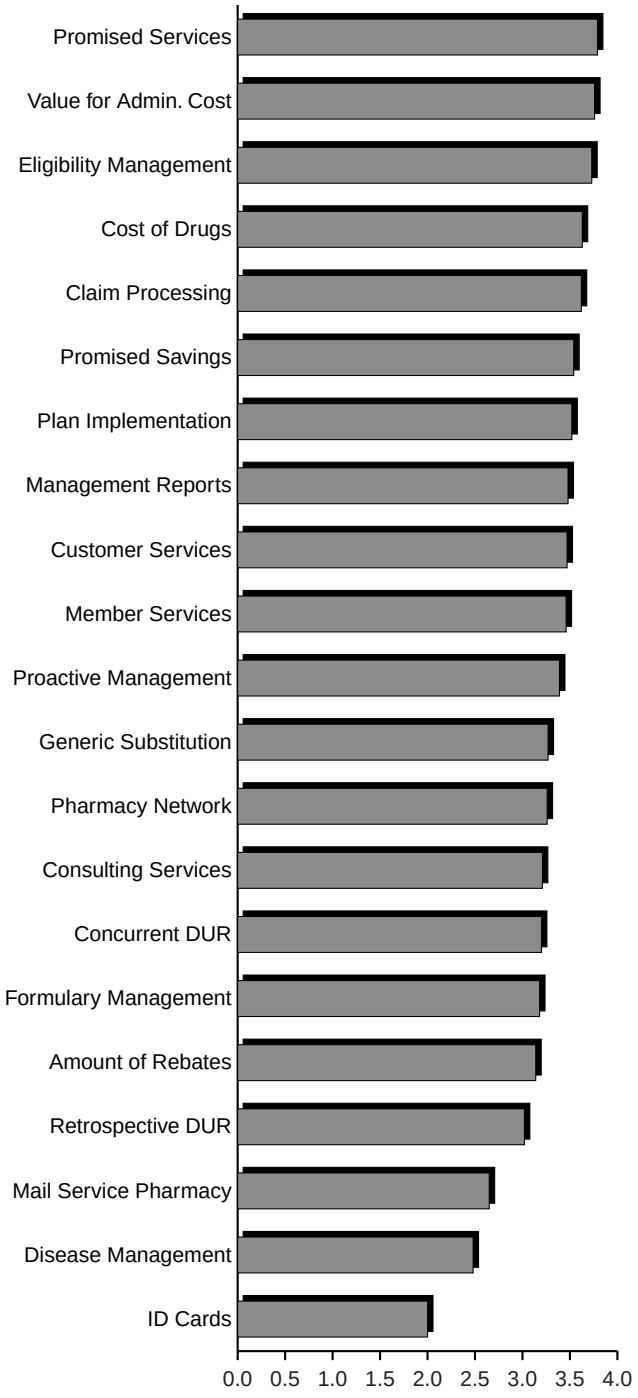
Source: Charts on pp. 62-64 are courtesy of the Pharmacy Benefit Management Institute in Scottsdale, AZ.



respondents indicated that they provided more positive responses to surveys conducted by their PBM or surveys conducted by some third-party with which their PBM contracted than they gave in response to PBMI's survey," the survey report states.

But that notion, if accurate, does give weight to other sections of the 42-page survey, primarily the individual performance scores given to nine of the country's largest PBMs: Caremark Prescription Service, Diversified Pharmaceutical Services, Express Scripts / ValuRx, Merck-Medco Managed Care Inc., National Prescription Administrators, PCS Health Systems, Advance Paradigm, Aetna Pharmacy Management, and Eckerd Health Services. **(See next page for more information.)** ■

HMO Importance Ratings of PBM Services



For More Information

❑ For more details or a copy of the complete survey, contact **Michael Deskin**, President, Pharmacy Benefit Management Institute, P.O. Box 9427, Scottsdale, AZ 85252-9427. Phone: (602) 730-0814.

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