Louisiana Medicaid

# Provider Update

Volume 24, Issue 6 November/December 2007

## All Providers

### Payment Error Rate Measurement

The Improper Payments Information Act of 2002 directs Federal agency heads, in accordance with the Office of Management and Budget (OMB) guidance, to annually review its programs that are susceptible to significant erroneous payments and report the improper payment estimates to Congress. OMB identified the Medicaid and the State Children's Health Insurance Program (SCHIP) as programs at risk for significant erroneous payments.

The Centers for Medicare and Medicaid Services (CMS) will measure the accuracy of Medicaid and SCHIP payments made by states for services rendered to recipients through the Payment Error Rate Measurement (PERM) Program. Under the PERM Program, CMS will use three national contractors to measure improper payments in Medicaid and SCHIP. As the statistical contractor, The Lewin Group will provide support to the program by identifying the claims to be reviewed and calculating each state's error rate. As the documentation/database contractor, Livanta LLC will collect medical policies from the state and medical records from providers. As the review contractor, HealthDataInsights, Inc. will perform medical and data processing reviews of the selected claims in order to identify any improper payments.

Medical records are needed to support medical reviews that the review contractor will conduct on the fee-for-service Medicaid and SCHIP claims to determine if the claims were correctly paid. If a claim is selected in a sample for a service that you rendered to either a Medicaid or SCHIP recipient, Livanta LLC will contact you for a copy of your medical records to support the medical review of the claim.

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Understandably, providers are concerned with maintaining the privacy of patient information. However, providers are required by Section 1902(a)(27) of the Social Security Act to retain records necessary to disclose the extent of services provided to individuals receiving assistance and furnish CMS with information regarding any payments claimed by the provider for rendering services. The furnishing of information includes medical records. In addition, the collection and review of protected health information contained in individual-level medical records for payment review purposes is permissible by the Health Insurance Portability and Accountability Act of 1996 and implementing regulations at 45 Code of Federal Regulations, parts 160 and 164.

It is important that you cooperate by submitting all requested documentations in a timely manner because failure to respond or insufficient documentation will count against the State as an error. Past studies have shown that the largest cause of error in medical reviews is no documentation or insufficient documentation. As such, it is important that information be sent in a timely and complete manner. Please note that LAMedicaid/Unisys will not reimburse providers for copying costs.

If you receive a request for medical records from Livanta LLC and have any questions concerning their request, please contact Deanie Vincent, LA Medicaid, at (225) 219-4149 or Robin Reed, Livanta's Medical Record Manager, at (301) 957-2380. Thank you for your support of the PERM Program.

## National Provider Identifier (NPI)

Implementation of National Provider Identifiers (NPI) is underway. The following important information is for all Medicaid providers who perform medical services and must obtain an NPI.

**Applying for Your NPI:**

If you are eligible for an NPI, you must apply online at: https://www.nppes.cms.hhs.gov/NPPES or request a paper application by calling: 1-800-465-3203. NPIs are assigned by the Centers for Medicare and Medicaid Services (CMS) enumerator.

**Louisiana Medicaid encourages providers to get one NPI for each Medicaid provider number (a one-to-one match).**

**Registering Your NPI with LA Medicaid:**

It is necessary to register your NPI with LA Medicaid as this information is not transmitted automatically from the enumerator. You may register online at www.lamedicaid.com (under NPI on the secured provider site) or complete the paper NPI registration form accompanying this notice and fax it to 225/216-6495. (This form is also available for download from the public side of our web site.)

Pharmacy providers were asked to provide their NPI with the annual POS recertification through the LA Medicaid Pharmacy Program. If you did not give this information at that time, please do so now.

There may be situations where it is necessary for providers to obtain and register one NPI for many Medicaid ID numbers OR multiple NPIs for one Medicaid ID number. In these cases, or if you need assistance with the registration process, please contact the LA NPI Assistance Hot Line at 225/216-6400 or e-mail LAMedicaidNPI@Unisys.com for assistance.

**In order to ensure that there is no interruption in your Medicaid payments you must apply, receive, and register your NPI(s).**

**Use of NPI for Pharmacy POS Claims Processing:**

LA Medicaid now processes Pharmacy claims submitted through Point of Sale (POS) using the pharmacy NPI instead of the LA Medicaid provider number if the NPI is registered with LA Medicaid.

**Use of NPI for Other Providers:**

Providers that bill using the electronic 837P, 837I, 837D, the revised CMS 1500 (08/05), ADA, or UB-04 claim forms may begin entering their NPIs **in addition to their 7-digit LA Medicaid ID numbers** in the appropriate locations on transmittals/claims submitted to LA Medicaid.

**At this time, providers must continue to submit claims with 7-digit Medicaid ID numbers.**

**Display of NPIs on Remittance Advices (RAs):**

If providers have registered their NPI(s) with LA Medicaid, the NPI(s) now appears on the weekly RA. The billing provider NPI appears in the upper left corner of the page immediately following the Medicaid ID number **if** the NPI is registered. The attending/servicing provider NPI appears to the right of the current Medicaid attending provider number field **if** the NPI is transmitted on the claim submitted to Medicaid.

Providers are asked to review all NPIs displayed on the weekly RA to ensure that the number is accurate for the corresponding billing/attending Medicaid provider number. Any discrepancies should be reported to the LA NPI Assistance Hot Line indicated above.

Questions or concerns related to the LA Medicaid implementation of NPI should be directed to the LA NPI Assistance Hot Line.

## Electronic Health Records Are Private, Secure and Efficient

*The following article appeared in the November issue of the Department of Health and Hospitals (DHH) Employee Newsletter:*

A report by the United States Department of Health and Human Services found that Louisiana is among only twelve states that are leading the country when it comes to adopting health information technology (HIT). These electronic health records have the potential to reduce health care costs, medical errors and inefficiency. However, recent studies have highlighted both these benefits and potential risks to patient privacy.

In October 2007, DHH Secretary Dr. Roxane A. Townsend helped to launch a new initiative to educate health care providers and Louisiana residents about how these electronic health records will be kept private and secure. Dr. Townsend joined other leaders from the Health Information Security and Privacy Collaboration to discuss this issue. Dr. Townsend said, "We're very proud to be at the forefront of implementing health information technology and on the cutting edge of how to keep data secure."

Already in Louisiana, DHH has sponsored several HIT projects. Pointe Coupee Parish received a $1.5 million grant to link 11 rural health care providers in the region. This comprehensive health information network is expected to improve the overall health care system and patient care. Another prominent project was the rural hospital pipeline, designed to link rural hospitals in North Louisiana to LSU Health Sciences Center in Shreveport. This venture may eventually include all the rural hospitals in the region.

One of the last barriers to implementing these technology initiatives, besides funding, is the privacy issue. According to Dr. Townsend, "Electronic health records are much safer than traditional paper documents. Electronic records require passwords for access and keep track of who has accessed the records. Of course, there are vulnerabilities, but we are working to put policies and procedures in place to mitigate those."

For more information on HIT initiatives, go to www.EHRtoday.org.

## Medicare Continues to Reduce Improper Claims Payments

The Centers for Medicare & Medicaid Services (CMS) announced today that aggressive oversight efforts have resulted in a further reduction of the number of improper Medicare claims payments, which declined from 14.2 percent in 1996, to 4.4 percent in 2006, to 3.9 percent in 2007. This solid improvement is a result of continued efforts initiated by CMS and its contractors to use detailed data analysis in targeting areas where erroneous claims processing, inaccurate billing and provider error result in waste, fraud and abuse.

"The decline in improper payments reflects our emphasis on identifying and eliminating waste, fraud and abuse in all CMS programs. It is critical that we ensure every dollar is spent wisely so that the program is affordable for taxpayers and future generations of beneficiaries," said CMS Acting Administrator Kerry Weems. The Medicare fee-for-service (FFS) error rate has declined from 14.2 percent in 1996, when the Medicare improper payment rate was first reported, to the current 3.9 percent in 2007. During the past three years, recent error rate reductions have led to approximately $11 billion less in improper payments. CMS pays more than 1 billion fee-for-service claims each year.

CMS conducted detailed reviews of randomly sampled Medicare FFS claims submitted between April 1, 2006 and March 31, 2007. Approximately 140,000 claims spanning all types of Medicare FFS payments were included in the Medicare error rate testing program. By providing accurate statistical information to its personnel and contractors, CMS can identify where problems exist and target improvement efforts to address the problems.

"This year's results show the commitment to use more detailed data and analysis to identify and eliminate improper payments is working. Protecting the integrity and ensuring the accountability of CMS programs is one of our fundamental responsibilities, and we're pleased with the improvement to the program," said Weems.

CMS has worked with its contractors to apply the data collected to improve claims processing system edits to ensure accurate billing, update coverage policies, and direct efforts to educate providers on how to avoid errors in areas with high improper payment rates. In addition, CMS has developed national and state-specific models for predicting inpatient-hospital payment errors in order to study the areas prone to payment error. These tools generate state-specific hospital billing reports that are used to target efforts to reduce payment errors.

CMS reports its Medicare FFS improper payment findings in an annual report released every November. The complete report contains additional error rate information along with more specific improper payment estimates. Once completed, the report will be posted at www.cms.hhs.gov/cert.

In addition to the Medicare error rate announcement, CMS also announced the preliminary results of the Payment Error Rate Measurement (PERM) Program developed for the Medicaid Program. This is the first year any component of Medicaid improper payments has been measured. The PERM review included in today's report was limited to only one of three Medicaid payment areas (Fee-For Service), 17 states, and reflects only the first two quarters of Fiscal Year 2006. Based on the limited data and the limited time period, CMS calculated that the preliminary Medicaid FFS component error rate was 18.5 percent.

As with the early experiences with the Medicare error rate beginning in 1997, the majority of this preliminary Medicaid FFS error rate is a result of insufficient documentation errors, meaning that all of the supporting documentation necessary to verify the accuracy of the claim was not provided. If all the supporting documentation had been received, the contractor could have determined whether the payment was appropriate or made in error.

For example, in Medicare, CMS worked to get to the root cause of insufficient documentation errors, resulting in insufficient documentation errors decreasing from 4.1 percent of the error rate in 2004 to 0.4 percent in 2007. The overall error rate was reduced by 61 percent during the same period of time.

CMS intends to work closely with the states to follow a similar approach with the Medicaid error rate measurement. CMS looks forward to continuing its partnership with the states on which there are Fiscal Year 2006 data to publish a full-year error rate in November 2008, working with them again in FY 2009 when CMS will measure improper payments in Medicaid and SCHIP fee for service, managed care, and eligibility.

## States Get Federal Backing to Build More Efficient, High Quality Medicaid Systems

*The following article appeared as a News Release on October 4, 2007 from the United States Department of Health & Human Services:*

Sixteen states and Puerto Rico have just been awarded nearly $52 million to fund research and design in new ways to improve Medicaid efficiency, economy and quality of care, Secretary Mike Leavitt announced. States will use the funds to implement innovative systems to get more value out of the money they spend providing health care to their low-income elderly, children and disabled citizens.

Congress approved a total of $150 million for these Medicaid "transformation grants" in the Deficit Reduction Act of 2005 (DRA) to be distributed over fiscal years 2007 and 2008. Today's award follows grants of $98 million that were distributed last January to 26 states.

"These transformation grants express the core goal of this administration to give states the kind of flexibility they need to deliver high quality care in an efficient and more economical way," Secretary Leavitt said.

# All Providers (Continued)

Transformation grants went to states with proposals that included:

- *Reducing patient error rates* through the implementation of interoperable health information technology (electronic health records, clinical decision support tools or e-prescribing programs)
- *Improving rates of collection from estates* of amounts owed under Medicaid
- *Reducing waste, fraud, and abuse* under Medicaid, such as reducing improper payment rates
- *Increasing the utilization of generic drugs* through education programs and other incentives. This reduces Medicaid expenditures for covered outpatient drugs, particularly in the categories of greatest drug utilization
- *Improving access* to primary and specialty physician care for the uninsured using integrated university-based hospital and clinic systems
- *Implementation of a medication risk management program* as part of a drug use review program

The awards granted today vary in amount depending on each state's application. No state matching funds are required for these special grants. More information on the grants can be found at: www.cms.hhs.gov/MedicaidTransGrants.

# Dental Service Providers

## EPSDT Dental Rate Increases and Delay in Payment Increases for Some Dental Services

Effective for **dates of service on and after November 1, 2007**, certain Medicaid-covered Early and Periodic Screening, Diagnosis and Treatment (EPSDT) Dental services will receive a reimbursement rate increase.The majority of dental claims related to the dental rate increase are being reimbursed at the new increased rates effective for dates of service on and after November 1, 2007. However, a delay in payment increases occured in the following situations**:**

- Amalgams, Primary Tooth (D2140, D2150 and D2160) will continue to pay at the fee on file as of October 31, 2007 until programming changes can be made. When programming changes are complete, Medicaid will automatically recycle all claims for primary teeth for procedure codes D2140, D2150 and D2160 with dates of service November 1, 2007 through the date of the programming change in order to correct payment.

- The fee for a second amalgam or resin-based restoration within a single 12-month period for the same patient, same tooth will continue to be cutback to the fee for the larger restoration on file as of October 31, 2007 until programming changes can be made. Once the programming changes are in place, Medicaid will automatically recycle all involved claims with dates of service November 1, 2007 through the date of the programming change in order to correct reimbursement.

- Refer to the document entitled "Dental Rate Increases and EPSDT Dental Policy Revisions Effective for Dates of Service on or after November 1, 2007" on the www.lamedicaid.com website under the "New Medicaid Information" link under the section for "Dental Providers". Reimbursement for the specific services detailed in this document that will be allowed once per six months are delayed until programming changes can be made. Until the programming changes are made, claims for these services when billed at the six month interval will deny. However, once the programming changes are in place, Medicaid will automatically recycle these claims with dates of service November 1, 2007 through the date of the programming change in order to provide reimbursement for these services.

Providers who bill their usual and customary fee as is required by Medicaid should not have to take any further action. Providers who do not bill their usual and customary fee will be responsible for their own claim adjustments. For complete fee information, please refer to the revised EPSDT Dental Fee Schedule with revision date November 1, 2007 which are located at **www.lamedicaid.com**.

## Medicare Project Shows Bed Sores Can Be Stopped in Nursing Homes with Proper Care

*The following article was a press release issued by the Centers for Medicare and Medicaid Services (CMS) Office of Public Affairs on October 22, 2007*:

A diligent and sustained focus on preventing serious bed sores in nursing home residents was remarkably effective according to the results of a project sponsored by the Centers for Medicare & Medicaid Services. Results of the project have just been published in the *Journal of the American Geriatrics Society.*

"Reducing pressure ulcers, the clinical term for bed sores, is a priority for CMS and quality improvement organizations (QIOs) nationwide," said Kerry Weems, acting administrator of CMS. "It is also one of the most important goals of the voluntary *Advancing Excellence in America's Nursing Homes* campaign, of which CMS is a founding member.

The nationwide project stopped more than two-thirds of the residents' serious bed sores, a dreaded complication of frailty and disability in old age, in the 35 nursing homes that reported data from the project, the paper reports.

"This project showed clinicians and managers that major improvement is possible, even for conditions affecting our most frail beneficiaries," added Barry M. Straube, MD, CMS chief medical officer and director of the Office of Clinical Standards and Quality. "The results will enable us to separate the serious pressure ulcers from the superficial ones, a change that will help beneficiaries and their families to see whether a nursing home has implemented the best practices available."

The publication reflects findings that stem from a collaboration among 52 nursing homes in 39 states, working voluntarily with experts on process improvement and preventing pressure ulcers. Participating facilities found that the onset of new serious bed sores (the ones that go through the skin and often to the bone) declined 69 percent.

"This is a remarkable gain in a large number of facilities, against a condition that is as devastating and costly as it has been resistant to improvement," said Weems. "In this case, the work of Medicare's Quality Improvement Organizations (QIOs) has helped us refocus our research and change our data collection and public reporting so that CMS can do a better job informing residents, family members, and the nursing homes themselves about nursing home quality.

Because serious bed sores often develop before a patient enters a nursing home, the project's teams often encouraged hospitals, home health agencies and emergency services to collaborate in order to identify and reduce causes of bed sores. The project also found that direct care providers, often certified nursing assistants, could be effective leaders of quality improvement efforts.

# Nursing Home Providers (Continued)

"This kind of project shows how valuable Medicare can be as a responsible public health agency and much more than just a payer of healthcare services," said Weems. "CMS aims to continuously improve care, learn and share the methods that improve care, and inform providers and the public about changes that can become standards for quality of care."

Qualis Health, the QIO for Washington State, coordinated the project for CMS. The QIO Program consists of 53 independent organizations under contract with CMS and is a key component in CMS' efforts to improve quality in nursing homes and other healthcare settings including hospitals, home health agencies and physician offices.

The improvement materials used in this project are available to anyone interested in improving the care of bed sores, free of charge, on the Medicare Quality Improvement Web site at: www.medqic.org (under the "Nursing Home" tab).

For more information on the voluntary campaign and its eight quality improvement goals, visit www.nhqualitycampaign.org.

# Mental Health Service Providers

## Central Louisiana State Hospital Partners with Volunteers of America on Pathways Shelter

*This article appeared in the November issue of the Department of Health and Hospitals (DHH) Employee Newsletter:*

On November 20, 2007, Pathways, a new shelter for the mentally ill, opened on the grounds of the Central Louisiana State Hospital in Pineville. The hospital provides acute, intermediate and long-term mental health care, treatment and rehabilitative services to children, adolescents and adults.

Many times, individuals with mental illness need intervention, but their crisis is not severe enough for them to be hospitalized or jailed. This new facility, operated by Volunteers of America, will provide a safe place for them to go. The shelter, the only one of its kind in the area, "will give law enforcement and health care workers a new option for mental health clients that they come across," said Machelle Vizia, program manager for Adult Mental Health Services at Volunteers of America. "The purpose of this shelter is to assist mental health clients in a time of crisis."

The facility has eight beds to house men and women with a mental illness that might not otherwise have anywhere else to go. An average stay at Pathways will be five to seven days, with the ultimate goal of finding housing for each client, whether it's transitional or permanent housing.

Referrals for the shelter come through the Mental Health Center, law enforcement, hospitals, crises intervention team officers and other mental health agencies. The shelter is available and open 24 hours a day, seven days a week, including holidays in order to meet the community's needs.

# Hospice Services Providers

## Hospice Policy Clarification

The following information clarifies Hospice Program Policy regarding signature and forms requirements:

- In cases where a patient signs the Notice of Election form with an "X"; there must be two witnesses to sign next to his/her mark.
- Hospice services will end when a patient's Medicaid eligibility ends. A new Notice of Election form and Certificate of Terminal Illness form is required with updated signatures whenever he/she is recertified for Medicaid. Providers are encouraged to contact family members regarding the patient's Medicaid coverage.
- Two different signatures are required on the Certificate of Terminal Illness form for persons receiving Medicaid only benefits, an Admitting/Attending Physician and the Hospice Medical Director or referring physician. This requirement is for the initial certification only.
- The patient's or the authorized representative's signature is required whenever a patient receiving "Medicaid only" revokes hospice.
- Hospice providers are no longer allowed to alter/revise the Medicaid Hospice forms. All providers must use the official forms printed in the Hospice Manual or the 2006 Hospice Training Packet.

# RA Message Corner

## Rate Increase for Extended Nursing Services

The Department of Health and Hospitals (DHH) is pleased to announce effective for dates of service on or after July 20, 2007, the reimbursement rates for extended nursing services have been increased as follows:

- S9123-Nursing care in the home performed by a registered nurse (RN) is increased to $34.00 per hour.
- S9124-Nursing care in the home performed by a licensed practical nurse (LPN) is increased to $32.00 per hour.
- S9123 TT-Nursing care for multiple recipients in the home performed by a registered nurse (RN) is increased to $17.00 per hour.
- S9124 TT-Nursing care for multiple recipients in the home performed by a licensed practical nurse (LPN) is increased to $16.00 per hour.

## Specialty/Subspecialty Update

To allow appropriate claims processing when reimbursement is based on specialty/subspecialty, individual providers are encouraged to confirm that their Medicaid provider file accurately reflects their specialty/subspecialty. If changes are required, the ***Provider Enrollment Specialty Change Form*** can be accessed online at www.lamedicaid.com, using links *Provider Enrollment* and *Forms to Update Existing Provider Information* respectively.

Completed forms should be mailed to:

Unisys Provider Enrollment Unit
Post Office Box 80159
Baton Rouge, LA 70898-0159

## Outpatient Psychiatric Services Codes

Effective with date of service October 1, 2007, Louisiana Medicaid reimburses for select procedure codes specific to outpatient psychiatric services. Detailed policy information will be forthcoming. Providers are asked to hold claims for these services until notified by the Department as programming is not yet complete. It is anticipated that the system changes will be in place in the near future. Please monitor future RA messages which will inform providers when these claims may be submitted.

## Immunization Administration Codes Update

Immunization administration Current Procedural Terminology (CPT) codes 90465-90648, 90473, and 90474 have been made payable and added to the current claims processing system. Providers should refer to the CPT code description to determine the appropriate code for the administration of a vaccine. Updated information regarding use of these codes can be found in the 2007 Provider Training materials for KIDMED and Professional Services.

Previously denied claims for these immunization administration codes will be systematically recycled from dates of service January 1, 2006 forward. Providers will be notified by RA messages when this recycle of denied claims is complete.

## Adult Immunizations Update

Effective with date of service October 1, 2007, Louisiana Medicaid reimburses for immunizations (vaccine and administration) to recipients age 21 years and older for Influenza, Pneumococcal, and Human Papilloma virus (HPV) diseases. Detailed policy information will be forthcoming. Providers are asked to hold claims for these services until notified by the Department of Health and Hospitals as programming is not yet complete. It is anticipated that the system changes will be in place in the near future. Please monitor future RA messages which will inform providers when these claims may be submitted.

## The Deficit Reduction Act of 2005, Section 6032 Implementation

As a condition of payment for goods, services and supplies provided to recipients of the Medicaid Program, providers and entities must comply with the False Claims Act employee training and policy requirements in 1902(a)(68) of the Social Security Act, set forth in that subsection and as the Secretary of the U.S. Department of Health and Human Services may specify. As an enrolled provider/entity, it is your obligation to inform all of your employees and affiliates of the provisions of the Federal False Claims Act, and any Louisiana laws and/or rules pertaining to civil or criminal penalties for false claims and statements, and whistleblower protections under such laws and/or rules. When monitored or audited, you will be required to show evidence of compliance with this requirement.

This provision requires any entity that receives annual Medicaid payments under the State Plan of at least $5 million to provide Federal False Claims Act education to their employees.

## MSA Code Changes

Effective with dates of service beginning October 1, 2007, the Metropolitan Statistical Assignment (MSA) codes currently used for billing hospice services in the following parishes have been changed to:

| | | | |
|---|---|---|---|
| Cameron-3960 | Grant-0220 | Desoto-7680 | E. Feliciana-0760 |
| Iberville -0760 | Pointe Coupee-0760 | St. Helena-0760 | Union-5200 |

# *The Use of Drugs Affecting the Renin Angiotensin System in the Management of Hypertension*

**By: Brice A. Labruzzo, Pharm.D.**
**Assistant Professor**
**College of Pharmacy**
**University of Louisiana at Monroe**

## Introduction

The Renin Angiotensin System (RAS) plays a significant role in the pathophysiology of a variety of disease states including hypertension, heart failure, myocardial infarction, and nephropathy.[1] Until recently, the Angiotensin Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Antagonists or Blockers (ARBs) were the only approved drug classes directly affecting the RAS. On March 5, 2007 the FDA approved aliskiren, an oral antihypertensive agent in a new class of drugs also affecting the RAS. This new class is referred to as the direct renin inhibitors and they are the newest antihypertensive class to be approved within the past ten years.

## Pharmacology

In order to understand the pharmacology of these drug classes, it is important to understand how the RAS works (page 17 figure). Renin is a circulating enzyme which is synthesized, stored, and released by juxtaglomerular cells in the kidney. Renin is the enzyme responsible for catalyzing the rate limiting step of the RAS pathway. Angiotensinogen, a substrate of renin, is cleaved into angiotensin (Ang) I. The next step in the pathway occurs when angiotensin converting enzyme cleaves Ang I into Ang II. Ang II increases total peripheral resistance by acting as a direct vasoconstrictor and has an effect on myocardial hypertrophy and remodeling. Additionally, Ang II affects renal function through its effects on sodium reabsorption, aldosterone release, and decreasing renal blood flow. These actions occur when Ang II binds to either the angiotensin type one ($AT_1$) receptor or the angiotensin type two ($AT_2$) receptor. Most effects of angiotensin are due to the binding of angiotensin to the $AT_1$ receptor. The $AT_2$ receptor is generally considered cardioprotective; however, its functional role has so far been poorly defined.[1] Renin inhibitors directly influence the rate limiting step of the RAS; however, both ACE inhibitors and ARBs act during later stages of the pathway. The ACE inhibitors interrupt the RAS by competitively inhibiting ACE which leads to decreased production of Ang II. While this causes some of the antihypertensive effects seen with ACE inhibitors, it is not the only mechanism. Additional benefits may be due to the increase in bradykinin levels. ACE is structurally identical to kinase II which inactivates kinins; therefore, inhibiting ACE potentiates kinin activity (e.g., bradykinin) which may lead to further blood pressure lowering effects through bradykinin's ability to cause vasodilation.[2,3] The ARBs have similar effects to the ACE inhibitors, but exhibit their effect even later in the pathway. Instead of inhibiting an enzyme, they competitively bind to the $AT_1$ receptor, thus inhibiting most biological effects of Ang II. Although ACE inhibitors have the potential to reduce the effect of Ang II on the $AT_1$ and $AT_2$ receptors, it is the

ARBs which mainly lower blood pressure by binding directly to the $AT_1$ receptor. The production of Ang II may be catalyzed by enzymes other than ACE that are present in the heart and possibly other areas of the body. For example, chymase, a serine protease, has been associated with ACE independent production of Ang II in human arteries.[4] ARBs can inhibit the effect of the Ang II produced through this pathway where the ACE inhibitors can not.

**Antihypertensive Response**

In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), approximately 1,800 (61% of participants) hypertensive patients 55 years or older with one or more risk factors for coronary heart disease treated with the ACE inhibitor lisinopril for five years reached their blood pressure goal of < 140/90 ($P<0.001$).[5] Data has shown that ACE inhibitors appear to be less effective in black patients when compared to their use in Caucasians. According to Materson et al, the response rates in black patients over the age of sixty taking the calcium channel blocker diltiazem or hydrochlorthiazide were higher than those taking the ACE inhibitor captopril.[6] As part of the ALLHAT study, high risk hypertensive patients were randomly assigned to the calcium channel blocker amlodipine or the ACE inhibitor lisinopril. In this study, black patients responded better to amlodipine than lisinopril.[7] Despite ACE inhibitor monotherapy having a poor response in black patients, the addition of a thiazide diuretic leads to blood pressure lowering effects similar to that seen in Caucasian patients.[8]

In a small study comparing efficacy and tolerability of the ARB losartan versus atenolol in patients with mild to moderate hypertension, losartan lowered systolic blood pressure (SBP) 11.4 mmHg after twelve weeks of treatment and diastolic blood pressure (DBP) 8.6 mmHg. There was no significant difference between atenolol and losartan blood pressure lowering effects.[9] In the Losartan Intervention For Endpoint reduction in hypertension study (LIFE), losartan was compared to the beta blocker atenolol in order to evaluate both morbidity and mortality in patients with hypertension and left ventricular hypertrophy. Approximately 9,000 patients were monitored in this randomized, double blind study. In this study, patients taking atenolol encountered a mean SBP lowering effect of 29.1 mmHg and patients in the losartan group had a mean SBP lowering effect of 30.2 mmHg. Despite this comparable decrease in blood pressure, patients in the losartan group experienced less cardiovascular mortality, myocardial infarction, and stroke ($p=0.021$).[10] In a study comparing the efficacy of olmesartan, losartan, valsartan, and irbesartan, researchers reported a 24-hour systolic blood pressure decrease of 8.1-12.5 mmHg and a diastolic decrease of 5.6-8.5 mmHg with olmesartan having the greatest effect, followed (in order) by irbesartan, losartan and valsartan.[11] Newer members of the ARB class, for example candesartan, telmisartan, and olmesartan, may be more effective in controlling hypertension than valsartan and other older agents.

A study published in 2005 reported alsikerin 150 mg to be as effective as 150 mg of the ARB, irbesartan, in patients with mild to moderate essential hypertension.[12] In a review article comparing five trials evaluating aliskiren monotherapy, systolic blood pressure decreases ranged from 8 mmHg to 15.8 mmHg and diastolic blood pressure decreases ranged from 4.5 mmHg to 11.8 mmHg.[13] This is similar to decreases in blood pressure seen with both ACE inhibitors and ARBs.

**Adverse Effects and Contraindications**

Adverse effects exhibited by ACE inhibitors, ARBs, and renin inhibitors are typically caused by the blockade of the RAS system. With ACE inhibitors, the increase in bradykinin also plays an important role in adverse effects. All drugs acting on the RAS pathway have a black box warning stating injury and death may occur to the developing fetus when used in the second and third trimesters.[14] Hypotension is a possible adverse effect with each of these drugs, but is usually only a concern in patients with heart failure or who are volume depleted. Hyperkalemia is also possible with all three of the RAS drug classes and is mainly due to the decrease in aldosterone concentrations, which plays a role in the urinary excretion of potassium. Other factors which can lead to hyperkalemia are dietary potassium intake (sometimes due to the use of potassium containing salt substitutes), other medical conditions, as well as, drug-drug interactions. Medical conditions increasing the chances of experiencing hyperkalemia include renal impairment and hypoaldosteronism. Concurrent use of either ACE inhibitors, ARBs, or renin inhibitors with the following drugs can also contribute to worsening hyperkalemia: NSAIDs, COX-2 inhibitors, immunosuppressants, and potassium sparing diuretics.[15] A decrease in Ang II has been associated with a decline in glomerular filtration rate (GFR) which can lead to a decline in renal function in some patients. [16] Because of this, patients' renal function should be monitored after initiation with one of these drugs. Both ACE inhibitors and ARBs are contraindicated in patients with bilateral renal artery stenosis. Renal artery stenosis (RAS) can lead to renal ischemia due to decreased afferent artery blood flow. In patients with RAS, GFR is maintained through vasoconstriction caused by Ang II. By blocking this Ang II-mediated vasoconstriction, decreased GFR will result.[17] Adverse effects of ACE inhibitors include dry cough and angioedema, occurring as a result of an increase in bradykinin. A dry cough develops in about 5 to 20% of patients taking an ACE inhibitor and is more commonly seen in women patients. Although angioneurotic edema (angioedema) only occurs in 0.1% to 0.2% of patients taking ACE inhibitors, it can be a life threatening adverse effect of these drugs.[18] Even though bradykinin levels are not increased with the use of ARBs or renin inhibitors, several cases of both cough and angioedema have been reported. A history of angioedema is a contraindication to the use of both ACE inhibitors and ARBs. Although aliskiren has no listed contraindications, it should be used cautiously in patients with a history of angioedema since its effects on bradykinin are currently unknown. The most common adverse effects reported with alsikerin use are headache, dizziness and diarrhea. These effects appear to be dose related.[15]

**Conclusion**

ACE inhibitors and ARBs are currently recommended for their blood pressure lowering effects in patients with Stage I and Stage II hypertension, especially for those with compelling indications such as diabetes, heart failure, coronary artery disease, and chronic kidney disease.[19] Although aliskiren appears to have less side effects associated with it and similar blood pressure lowering effects to the ACE inhibitors and ARBs, its place in therapy is currently undefined. No available data on long term morbidity or mortality effects with aliskiren exists at this time; however, there are currently several phase III trials assessing aliskiren's effect on diabetic nephropathy, heart failure, and left ventricular hypertrophy. Perhaps when the data from these trials are released, clinicians will have a better idea whether or not renin inhibitors should also be considered a preferred antihypertensive agent when considering a drug that can lower blood pressure, as well as, prevent end organ damage.

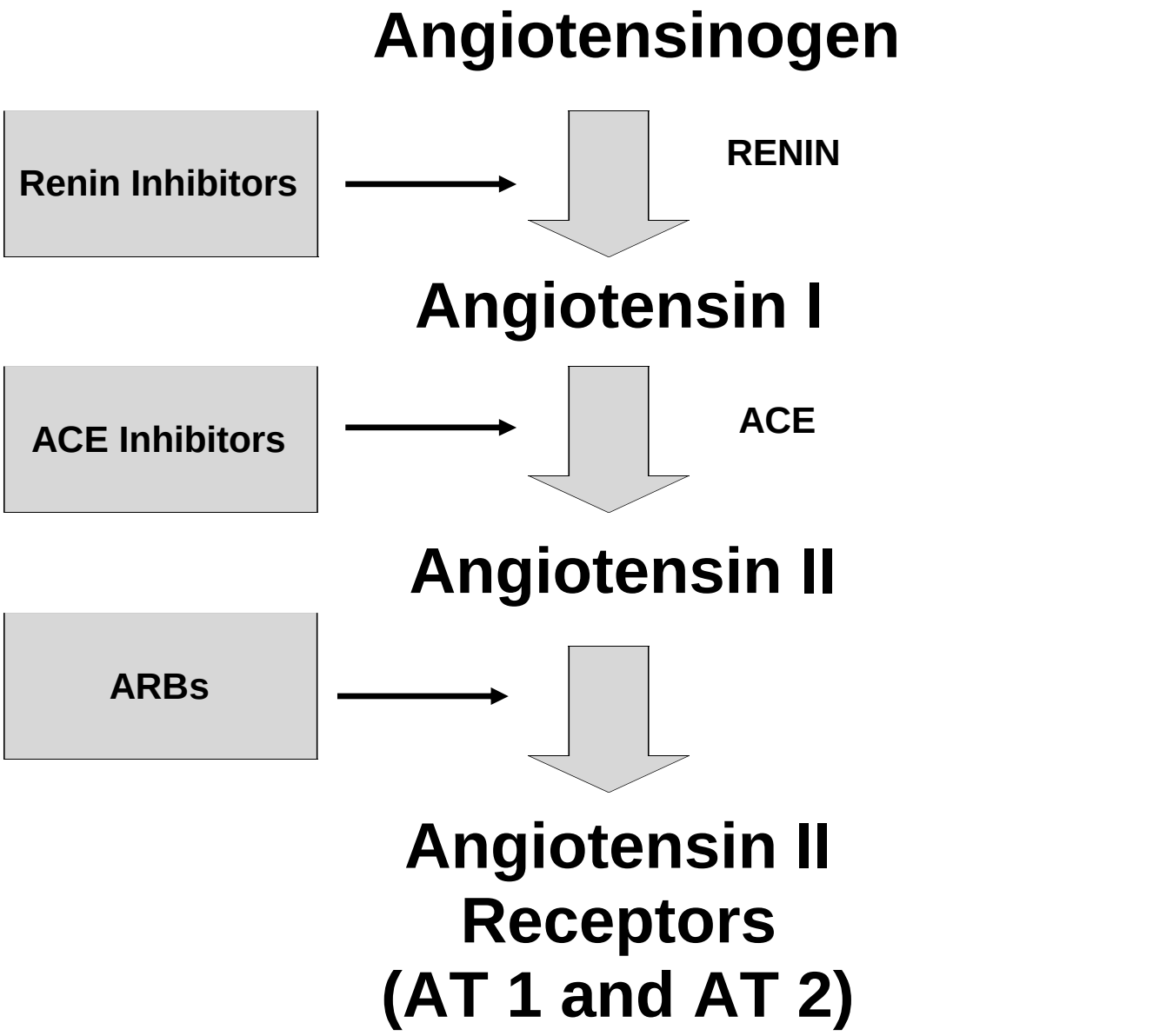
Angiotensinogen
Renin Inhibitors
RENIN
Angiotensin I
ACE Inhibitors
ACE
Angiotensin II
ARBs
Angiotensin II Receptors (AT 1 and AT 2)

**Table 1: ACE Inhibitors Available in the United States [20]**

| Generic Name | Trade Name | Available Strengths (mg) | Usual Adult Maintenance Dose | Generic Available |
|---|---|---|---|---|
| Benazepril | Lotensin® | 5, 10, 20, 40 | 20-40 mg in 1-2 divided doses | Yes |
| Captopril | Capoten® | 12.5, 25, 50, 100 | 12.5-150 mg 2-3 times per day | Yes |
| Enalapril | Vasotec® | 2.5, 5, 10, 20 | 5-40 mg in 1-2 divided doses | Yes |
| Fosinopril | Monopril® | 10, 20, 40 | 20-40 mg in 1-2 divided doses | Yes |
| Lisinopril | Prinivil®/Zestril® | 2.5, 5, 10, 20, 30, 40 | 10-40 mg in 1-2 divided doses | Yes |
| Moexipril | Univasc® | 7.5, 15 | 7.5-30 mg in 1-2 divided doses | No |
| Perindopril | Aceon® | 2, 4, 8 | 4-16 mg in 1-2 divided doses | No |
| Quinapril | Accupril® | 5, 10, 20, 40 | 10-40 mg once daily | Yes |
| Ramipril | Altace® | 1.25, 2.5, 5, 10 | 2.5-5 mg once daily | No |
| Trandolapril | Mavik® | 1, 2, 4 | 1-4 mg once daily | Yes |

**Table 2: ARBs Available in the United States [21]**

| Generic Name | Trade Name (manufacturer) | Available Strengths (mg) | Usual Adult Maintenance Dose | Generic Available |
|---|---|---|---|---|
| Candesartan | Atacand® | 4, 8, 16, 32 | 4-32 mg once daily | No |
| Eprosartan | Teveten® | 400, 600 | 400-800 mg in 1-2 divided doses | No |
| Irbesartan | Avapro® | 75, 150, 300 | 150-300 mg once daily | No |
| Losartan | Cozaar® | 25, 50, 100 | 50-100 mg in 1-2 divided doses | No |
| Olmesartan | Benicar® | 5, 20, 40 | 20-40 mg once daily | No |
| Telmisartan | Micardis® | 20, 40, 80 | 20-80 mg once daily | No |
| Valsartan | Diovan® | 40, 80, 160, 320 | 80-320 mg once daily | No |

**Table 3: Direct Renin Inhibitor Available in the United States[14]**

| Generic Name | Trade Name (manufacturer) | Available Strengths (mg) | Usual Adult Maintenance Dose | Generic Available |
|---|---|---|---|---|
| Aliskiren | Tekturna® | 150, 300 | 150-300 mg daily | No |

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