Antihypertensive drugs for the management and treatment of hypertensive disorders of pregnancy

Technology Opportunity Assessment

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## Acronyms and abbreviations

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<th>Definition</th>
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<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
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<td>ARBs</td>
<td>angiotensin receptor-blocking drugs</td>
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<td>BP</td>
<td>blood pressure</td>
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<td>CLIP</td>
<td>Community Level Interventions for Pre-eclampsia</td>
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<td>dBp</td>
<td>diastolic blood pressure</td>
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<td>DEEP</td>
<td>Digibind® Efficacy Evaluation in Preeclampsia</td>
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<td>DIF</td>
<td>digoxin antibody fragment</td>
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<td>EDLF</td>
<td>endogenous digoxin-like factors</td>
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<td>EML</td>
<td>Essential Medicines List</td>
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<td>HDP</td>
<td>hypertensive disorders of pregnancy</td>
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<td>IV</td>
<td>intravenous</td>
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<td>LRS</td>
<td>low-resource settings</td>
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<tr>
<td>MCHIP</td>
<td>Maternal and Child Health Integrated Program</td>
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<tr>
<td>NICE</td>
<td>UK National Institute for Health and Clinical Excellence</td>
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<tr>
<td>PE</td>
<td>preeclampsia</td>
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<td>PE/E</td>
<td>preeclampsia and eclampsia</td>
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<tr>
<td>sBP</td>
<td>systolic blood pressure</td>
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<tr>
<td>SSA</td>
<td>sub-Saharan Africa</td>
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<tr>
<td>UN</td>
<td>United Nations</td>
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<tr>
<td>USAID</td>
<td>United States Agency for International Development</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Statement of need

Hypertension is the most common medical problem encountered during pregnancy, complicating approximately 10 percent of pregnancies. Preeclampsia and eclampsia (PE/E) account for about half of these cases worldwide. In Africa and Asia, nearly one-tenth of all maternal deaths are associated with hypertensive disorders of pregnancy (HDP), whereas one-quarter of maternal deaths in Latin America have been associated with those complications. HDP are also a major cause of severe maternal and perinatal morbidity and long-term disability.

The World Health Organization (WHO) classifies HDP as: hypertension without proteinuria (chronic and gestational), mild preeclampsia (PE), severe PE, and eclampsia. Chronic hypertension and gestational hypertension are relatively rare causes of maternal mortality. However, chronic or gestational hypertension can progress to PE. PE, in turn, may progress to severe PE and eclampsia, although if PE progresses, the rate of progression and the occurrence of serious complications are all difficult to predict. In some cases, mild PE progresses to severe PE and then eclampsia very suddenly, with little or no warning. In other cases, a woman may begin having eclamptic fits in the absence of hypertension and proteinuria. Eclampsia can occur during the antepartum, intrapartum, and postpartum periods, with 90 percent of eclampsia cases occurring after 28 weeks of gestation.

Factors affecting the decision to treat hypertension during pregnancy include the level of blood pressure (BP), the underlying etiology of the elevated blood pressure, and time until childbirth. A major goal of treatment of hypertension is to minimize the risk of cardiovascular or cerebrovascular events, placental abruption, and intrauterine growth restriction. In hypertensive pregnant or postpartum women, the target blood pressures are 130 to 150 mmHg systolic blood pressure (sBP) and 90 to 100 mmHg diastolic blood pressure (dBP). The decision to use antihypertensive therapy in women must, however, weigh benefits of reducing maternal risk with potential risks of exposing the fetus to potentially harmful physiological effects of these drugs, as all antihypertensive drugs cross the placenta. There is also evidence that, in some women, aggressive lowering of blood pressure, regardless of the type of hypertension or choice of medication, can significantly impair fetal growth.

Of all factors influencing the decision to initiate antihypertensive drug therapy, the level of blood pressure is the most important. Treatment of severe hypertension (sBP ≥160 mmHg and/or dBP ≥110 mmHg) has a well-established maternal benefit of reduction in stroke risk. Severe systolic hypertension may be the most important predictor of cerebral hemorrhage and infarction in these patients and, if not treated expeditiously, can result in maternal death. Maternal or fetal benefits from treatment of mild to moderate hypertension have not been demonstrated. Furthermore, there is little evidence that women are protected from PE by treating their mild and moderate hypertension during pregnancy. Unfortunately, the recommendations on when to initiate and terminate treatment for hypertension and the ranges for target BP differ widely. WHO only recommends treatment with antihypertensive drugs for severe hypertension during pregnancy.

In addition, the comparative efficacy of antihypertensive drugs in improving pregnancy outcome and fetal safety is not certain, and there are scarce data from large, well-designed randomized trials on which to base a strong recommendation for use of one drug over another.
drugs: hydralazine, calcium channel blockers (nifedipine, nimodipine, nicardipine, and isradipine), labetalol, methyldopa, diazoxide, nitroglycerin, prostacyclin, ketanserin, urapidil, magnesium sulfate, prazosin, and isosorbid. Based on their review of the evidence, the guideline development group felt that there was not enough evidence to recommend a particular antihypertensive drug or its route of administration for the treatment of hypertension during pregnancy. Instead, the WHO guidelines focus on treatment of severe hypertension and state the following: (1) the choice and route of administration of an antihypertensive drug for severe hypertension during pregnancy, in preference to others, should be based primarily on the prescribing clinician’s experience with that particular drug, its cost, and local availability; and (2) diuretics, particularly thiazides, are not recommended for the prevention of PE and its complications.3

The recommendations are ambiguous around when to initiate and terminate treatment, whether or not to treat mild and moderate hypertension, ideal target BP, management of BP in the postpartum period, and the most effective antihypertensive drug. This ambiguity makes development of clear, evidence-based recommendations for low-resource settings (LRS) extremely difficult. It is therefore essential to build evidence that differentiates and substantiates the effectiveness and safety of the leading antihypertensive drugs for use in pregnancy and the postpartum period. In addition, to increase access to the most effective drugs and modes of administration, additional measures must be undertaken such as inclusion in national clinical guidelines and national formularies and increased training on their use.

**Technology solutions landscape**

There is a broad range of antihypertensive drugs available for use during pregnancy. Guidelines are not clear and differ widely, and choices must be based on consideration of the underlying etiology of the disease, the presence of significant proteinuria, the level of severity of the hypertension, the timing of childbirth, and local availability of effective antihypertensive drugs. Antihypertensive therapy is most critical for the acute management of hypertension during pregnancy and the postpartum period, BP control during expectant management of severe PE/E, and ongoing management of chronic hypertension.

Antihypertensive drugs come in oral and intravenous (IV) dosage forms. The disadvantage of any IV treatment is that it requires a fair amount of skill, needles and syringes, sterile conditions, and reasonable access to the vein. Oral antihypertensive drugs are easier to administer, are readily available, and generally cost less.

**Antihypertensive drugs that can be safely used during pregnancy include:**

1. **Sympathetic nervous system inhibitor:** Alpha-adrenergic agonist: methyldopa.

   Methyldopa is widely used for long-term oral therapy, and is sometimes needed in preeclamptic women with severe hypertension remote from term. The drug’s long-term safety for the fetus has been well demonstrated, but recommendations suggest avoiding the use of methyldopa in the postpartum period because it can cause depression in some women. However, it is only a mild
anti hypertensive agent and has a slow onset of action (three to six hours), and therefore may be less effective for acute and severe hypertension.14

2. Direct vasodilators: hydralazine.

Hydralazine has been widely used for many years to manage acute hypertension in pregnancy or as a third-line agent for multidrug control of refractory hypertension. Despite having documented side effects (maternal hypotension and decreased blood flow to the fetus),10,15 the WHO midwifery education guide recommends use of IV hydralazine for management of hypertension in pregnancy.16 However, recent data on maternal and perinatal adverse effects associated with hydralazine have led some researchers to state that hydralazine should no longer be considered the antihypertensive medication of choice.17


Antihypertensive drugs with both alpha- and beta-adrenergic blocking activity may preserve uteroplacental blood flow to a greater extent than traditional beta-blockers. The UK National Institute for Health and Clinical Excellence (NICE) guidelines recommend oral labetalol for acute and severe hypertension and PE. Side effects may include maternal hypotension.8 A systematic review of the literature has shown that labetalol is the most promising drug to achieve a protective effect. To test its effectiveness, a randomized clinical trial is ongoing in Argentine hospitals.14

Although pindolol and metoprolol are less well studied in pregnant women, they are acceptable alternative antihypertensive drugs.18

4. Calcium channel blockers: isradipine, nifedipine (long-acting or immediate release), amlodipine, verapamil, diltiazem.

Calcium channel blockers appear to be safe for use in pregnancy.19 Nifedipine, in both immediate-release and long-acting forms, is widely used during pregnancy and is also recommended during lactation. There are sparse data on the use of amlodipine, verapamil, and diltiazem in pregnancy, but these are also used in pregnant patients.

Antihypertensive drugs that should be used with caution during pregnancy:

1. Peripherally acting adrenergic receptor antagonists:

   Nonselective beta-adrenergic blockers (e.g., propranolol) have been associated with premature labor, neonatal apnea, intrauterine growth restriction, bradycardia, and hypoglycemia. Beta-adrenergic blockers that lack alpha-blocking properties (e.g., atenolol) have been associated with lower placental and fetal weight at birth when used early in pregnancy. These drugs are therefore generally avoided if an effective drug with a better safety profile is available.20
In breastfeeding women, atenolol and labetalol are currently recommended, either individually or in combination.3

b. Alpha blocker: prazosin.

Prazosin has been used successfully in pregnancy without adverse effects. However, there are no adequate and well-controlled studies which establish the safety of prazosin hydrochloride in pregnant or lactating women.21

2. Direct vasodilator: nitroprusside.

A small study (22 pregnancies) showed the possibility of fetal cyanide poisoning with use of nitroprusside during pregnancy. Since then, use of nitroprusside has been restricted in pregnancy, although it can be used as the agent of last resort for urgent control of refractory severe hypertension if its use is limited to a short period of time.22

Antihypertensive drugs that should be avoided during pregnancy:

1. Diuretics: hydrochlorothiazide, furosemide, indapamide.

Diuretics reduce maternal plasma volume and can cause electrolyte disturbances. WHO recommends against the use of diuretics, particularly thiazides, for the prevention of PE and its complications.3 Diuretics are generally only used when women with PE develop pulmonary edema. Women with chronic hypertension and already on these treatments should have their regimen adjusted for pregnancy.

2. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor-blocking drugs (ARBs), and direct renin inhibitors: captopril, enalapril, perindopril.

ACE inhibitors, ARBs, and direct renin inhibitors are associated with significant fetal renal abnormalities when maternal exposure has been in the latter half of pregnancy, and with fetal cardiac abnormalities when maternal exposure has been in the first trimester.23

Most commonly used antihypertensive drugs in low-resource settings

Of all the antihypertensive medications available, labetalol, nifedipine, and hydralazine are most commonly recommended for acute management of severe HDP. Methyldopa continues to be recommended for long-term therapy. Table 1 lists the most commonly used antihypertensive drugs for HDP in LRS. * Recent research conducted by the Maternal and Child Health Integrated Program (MCHIP) indicates hydralazine and nifedipine are the most commonly available and used antihypertensives in 31

* The information in this table was adapted from the following sources:
countries representing LRS.²⁴ Follow-up studies to understand how decisions about choice of drugs are made in developing countries would help tailor recommendations to suit their needs.

Table 1. Most commonly used antihypertensive drugs for HDP in LRS

<table>
<thead>
<tr>
<th></th>
<th>Nifedipine</th>
<th>Labetalol</th>
<th>Hydralazine</th>
<th>Methyldopa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mode of action</strong></td>
<td>Calcium channel blocker causing dilatation of small arteries.</td>
<td>Combined alpha and beta-blocker.</td>
<td>Vasodilator</td>
<td>Alpha-adrenergic agonist</td>
</tr>
<tr>
<td><strong>Route of administration</strong></td>
<td>Oral</td>
<td>Oral, IV</td>
<td>Oral, IV</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Dose to manage: severe hypertension/PE/E</strong></td>
<td>Tablets recommended only; 10–30 mg orally, repeat in 45 min if needed.</td>
<td>20 mg IV, then 20–80 mg every 20–30 min, up to a maximum of 300 mg; or constant infusion of 1–2 mg/min.</td>
<td>5 mg, IV or IM, then 5–10 mg every 20–40 min; or constant infusion of 0.5–10 mg/h.</td>
<td>Currently not recommended for use with severe hypertension.</td>
</tr>
</tbody>
</table>

Another area that is poorly understood is the choice of antihypertensive drugs for hypertension in the postpartum period. There is consensus that antihypertensive therapy should be continued after delivery, but there is insufficient evidence to recommend any particular antihypertensive drug. BP can take up to three months to return to normal. During this time, BP should not be allowed to exceed 160/110 mmHg. As noted above, the recommendations suggest avoiding the use of methyldopa in the postnatal period because it can cause depression in some women. In breastfeeding women, labetalol, atenolol, and nifedipine are currently recommended, either individually or in combination.³ More evidence is needed to guide the development of clear guidelines for the treatment and management of postpartum women.

Finally, while research continues on currently administered antihypertensive drugs, additional drugs with antihypertensive properties and novel uses for hypertension are being investigated. Most of this research is in the very early stages of development. A few drugs have progressed to preclinical studies, but it is too early to assess the potential of these drugs as effective antihypertensive agents.†‡ The focus of this landscape is on currently available and recommended antihypertensive drugs for HDP. Potentially novel developments may be described in a future document.

One exception is the research on digoxin antibody fragment (DIF), which is farther along and has shown some promising results. DIF could affect PE by neutralizing endogenous digoxin-like factors (EDLF),

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† The antihypertensive compound olmesartan, an angiotensin type 1 receptor blocker, has been shown to reduce blood pressure in a PE model in mice. This is unlikely to lead to further pregnancy-induced hypertension research as sartans are contraindicated in pregnant women and can lead to fetal malformation. Available at: http://www.nature.com/hr/journal/v31/n12/pdf/hr2008274a.pdf.

‡ Studies have been conducted demonstrating the antihypertensive effects of aminopeptidase A (APA) in pregnant spontaneously hypertensive rats. The proposed mechanism of action for APA is the degradation of vasoactive peptides produced by the fetus as they cross the placental blood barrier. Available at: http://www.sciencedirect.com/science/article/pii/S0024320510004613.
which are produced by the placenta and are present at higher levels in some women with PE. This action could possibly halt the progression of the disease. The Digibind® Efficacy Evaluation in Pre-eclampsia (DEEP) study has been investigating whether the presence of DIF would affect the initiation of antihypertensive therapy or modification of dose or choice of drug. Digibind®, a commercially available anti-digoxin antibody approved for the treatment of digoxin intoxication, has been assessed in experimental models of hypertension with elevated EDLF levels. Digibind® has been shown to lower BP, suggesting that the antibody cross reacts with EDLF. These observations have led to the hypothesis that Digibind® might halt some of the manifestations of PE, especially hypertension. Based on these initial results, a clinical trial is planned to test the effect of Digibind® in severe PE. The study is a multisite, parallel, double-blind, placebo-controlled, randomized trial. Initial results are promising, but they are not conclusive, and further study will be required to assess the potential of this innovative intervention.

Gap analysis

Challenges and key barriers to widespread and effective use of antihypertensive drugs during pregnancy and the postpartum period:

1. **Insufficient clinical evidence on the most effective drug or combination of drugs.**

   The majority of studies on antihypertensive drugs evaluate existing drugs, combinations of drugs, and modes of administration. They are examining maternal and fetal outcomes to determine the most effective and safe drug to use for hypertension in pregnancy. However, many of these clinical studies have significant limitations, including small sample sizes, varied drug dosages, and negligible outcomes and maternal benefits. As a result, the quality of the evidence is low and conclusions and consensus on the most effective drugs have been difficult to reach.

   Clinical trials of regimens for the acute treatment of very high blood pressure (sBP ≥160 mmHg and/or dBP ≥110 mmHg) have generally used medications administered intravenously (e.g., hydralazine and labetalol). While these regimens are effective, they present certain challenges in LRS because they require intravenous access and may reduce blood pressure rapidly, potentially harming the fetus.

   Therefore, with many of the parenteral options, women require careful fetal monitoring, which may not be feasible in many LRS. A number of oral therapies are available and a few have been described in clinical practice, but no study comparing the various oral agents has yet been completed. Evidence of the relative risks and benefits of different oral regimens will help to develop the data to provide guidance for antihypertensive use in pregnancy, especially where multiple drugs are available. One promising study conducted by Gynuity Health Projects aims to assess and compare the efficacy of three oral agents: methyldopa, nifedipine, and labetalol. Efficacy is measured by the drugs reaching the target BP in six hours with minimal side effects and maternal and fetal outcomes. Oral agents would be more appropriate for use in low- and middle-income countries, as they are easier to administer than IV drugs and are generally less costly. This kind of evidence is critical to determine if one oral drug is more effective than another and if a combination of drugs must be used. Only a few

§ Digibind is a registered trademark of GlaxoSmithKline.
other clinical studies are currently ongoing, which might indicate a need for larger, more carefully
designed trials to address efficacy and safety of various antihypertensive drugs.

2. Lack of clear consensus on the most effective drug or combination of drugs.

Limited clinical evidence—particularly in LRS—has made it difficult to reach consensus on clear
guidelines for providers on: the optimal antihypertensive drug to use during pregnancy and the
postpartum period, when to initiate and terminate treatment, whether or not to treat mild and moderate
hypertension, what target BP should be, and how to manage BP in the postpartum period.
Recommendations differ and most guidelines are not drug-specific because feasibility of use depends
on setting and variables (e.g., cost, local availability, and local provider familiarity with the drug).
Until more conclusive evidence is available, WHO recommends that providers in developing
countries follow their national guidelines and choose antihypertensive drugs based on their
experience, the condition of the patient, their familiarity with the drug(s) and knowledge of side
effects, and availability of the drug in that context.11

3. Limited access to a supply of high-quality and low-cost antihypertensive drugs.

A recent survey in over 40 countries showed that the average availability of generic antihypertensive
drugs across all countries was 57 percent for the private sector and 35 percent for the public sector.29
High private-sector prices are caused by a manufacturer’s high selling price, taxes and tariffs, and
high mark-ups in the supply chain.31 According to the Research Triangle Institute (RTI) MANDATE
(Maternal and Neonatal Directed Assessment of Technology) model, a 25 percent penetration rate for
antihypertensive drugs in clinics and a 70 percent penetration rate in hospitals for sub-Saharan Africa
(SSA) and India were reported.** Lack of availability of the drugs in the public sector was attributed
largely to scarce resources, inaccurate demand forecasting, weak procurement, and weak distribution
channels. As a result, patients often have to pay higher prices to purchase the drugs from the private
sector, or forego use of the drugs.

The quality of antihypertensive drugs is another challenge in many LRS. Limited local production
compels countries to import a majority of the medicines, making it potentially harder to regulate. In
Nigeria, for example, manufacturers and suppliers have their own distribution channels, which results
in drugs sold in unregistered and unlicensed premises. It is estimated that 17 percent of essential
generic medicines as a whole are ineffective and counterfeit.32 Drugs of substandard quality are a
common problem. For example, a recent survey in Rwanda showed that 20 percent of hypertensive
medicines purchased in the market were of substandard content and 70 percent were of insufficient
stability.33 The sub-standard quality of drugs in Rwanda and elsewhere can be a result of (1) drugs
that are not manufactured with pharmaceutical-grade components and do not meet minimal quality
requirements, or (2) drugs that are compromised as a result of exposure to harsh environmental
conditions, including high temperatures and high humidity. Both high humidity and high
temperatures have deleterious effects on the majority of antihypertensive drug formulations.34 A
review of product information for ALDOMET™ (methyldopa),†† Procardia® (nifedipine),‡‡

†† ALDOMET is a registered trademark of Merck & Co., Inc.
‡‡ Procardia is a registered trademark of Pfizer, Inc.
Normozide® (labetalol),§§ and parenteral hydralazine all recommend storage in dry conditions away from sunshine and light at room temperature not to exceed 25ºC. 35–37

Finally, the cost of antihypertensive drugs is a barrier to widespread availability and use. Prices of medicines in most SSA countries are well above their production costs38–40 and the profits of those in the distribution chain (pharmacists, dispensing doctors, wholesalers, and even some governments) are frequently high. A 2008 United Nations (UN) report on SSA estimates that, in the public sector, generic medicines cost on average 250 percent more than the international reference price; in the private sector, those same medicines cost on average about 650 percent more than the international reference price.31 Patient prices of sampled antihypertensive medicines were even more expensive than estimated by the UN report, being on average 313 percent and 745 percent higher than international reference prices in the public and private sector, respectively. For example, nifedipine and methyldopa are both widely used in Nigeria. Both are manufactured locally and are available at lowest cost in the public sector and private pharmacies,32 but availability in the public sector is only around 62 percent. In Uganda, medicines are provided free of charge at public facilities but are still priced 2.6 times higher than the international reference price. One study found that the median availability of essential drugs at public facilities was 55 percent.41

Investment opportunity

There is still a fair amount of uncertainty surrounding the best choice of antihypertensive drugs for managing HDP. Efforts to increase the evidence base that would catalyze and support global action, leading to the development of a set of agreed-upon guidelines, are needed. In addition, efforts to increase and expand access to effective, low-cost antihypertensive drugs are also needed. Priority investment opportunities include:

1. **Conduct research to better understand and address the issues of limited access and availability of antihypertensive drugs by:**
   
   a. Identifying the key barriers to improved supply and distribution of antihypertensive drugs in a select number of countries. An opportunity to leverage the increasing interest of the UN Commission on Life-Saving Commodities for Women’s and Children’s Health in maternal health commodities and PE/E exists. Antihypertensive drugs could be included in the discussions about challenges to access of essential drugs. A desired result would be an assessment and advocacy plan that would provide specific and detailed information about the current challenges to availability and would outline strategies to increase access to antihypertensive drugs. Such advocacy efforts have been successful for other essential drugs and commodities (e.g., misoprostol). Engagement of key stakeholders at the global level and more focused assessment and policy efforts at the country levels could mobilize support for greater access to and integration of antihypertensive drugs into relevant policies and programs.
   
   b. Analyzing the cost of the most commonly used antihypertensive drugs and the factors that drive up the cost of the drugs that are orders of magnitude higher than international reference prices.

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§§ Normozide is a registered trademark of Schering Corporation.
Addressing cost would require a more in-depth look at the drivers of cost, an assessment of supply and demand challenges (from both providers and women with HDP), and understanding how countries choose and finance antihypertensive drugs for HDP.

c. Supporting ongoing in-country efforts to improve access and procurement practices for leading antihypertensive drugs. The investment opportunity would focus on development of a clear advocacy plan that would drive policy and national recommendations.

d. Supporting the use of national Essential Medicines Lists (EML) as advocacy tools. EMLs can serve as tools that advocate for the selection and use of the most effective drugs. According to a survey conducted in 30 countries by MCHIP, the four most widely recommended drugs for HDP (labetalol, hydralazine, nifedipine, and methyldopa) are largely approved through national policy and service delivery guidelines for administration as first-line antihypertensives in severe PE/E. These drugs, except for labetalol (likely due to its higher cost) are listed on these countries’ EMLs. This information might indicate that the largest barriers to use may lie in areas other than national policy, such as cost, availability, and provider awareness. Once the key barriers to access are identified, targeted promotion of the antihypertensive drugs listed on the EMLs could lead to increased use and availability of the drugs at lower cost. A study by Lalani et al. in 144 countries supports the MCHIP survey findings and concludes that antihypertensive drugs for use in pregnancy are available, but that EMLs need to be kept updated as they often included drugs that are no longer recommended because of safety or quality concerns. Drugs listed on the national EMLs are often lower cost and more aligned with global recommendations, and the EMLs should be used as a tool to promote the preferential use of certain drugs and support availability at lower cost.

2. **Analyze the prevalence of sub-standard antihypertensive drug quality, and make recommendations for appropriate approaches and tools to confirm quality and potency.**

Specific and accurate information about quality and stability of antihypertensive drugs is not widely accessible, and proprietary information about stability is not always publicly available. Determining whether quality is compromised as a result of: (a) exposure to heat and moisture due to ineffective packaging and storage conditions, or (b) use of sub-standard components by manufacturers, (c) counterfeit drugs, or (d) a combination of the above, is challenging. Furthermore, in many LRS, where regulatory oversight is weak, the problem, if identified, cannot always be easily addressed.

This investment opportunity would focus on gathering information in a few selected countries to characterize the magnitude of the problem and on developing a strategy to address the issue of quality. These quality assessment studies could be modeled after the oxytocin studies undertaken by PATH in Africa. A starting point would be a small study that would sample antihypertensive drugs in selected countries to assess quality of the drugs. These activities could be launched in priority countries of the UN Commission on Life-Saving Commodities, linking this effort to the larger drug quality program under the work of the Commission. Antihypertensive drugs for HDP are not currently on the list of life-saving commodities. Joining the UN Commission’s drug quality efforts, which are in the early stages of development, would ensure that antihypertensive drugs for HDP are part of the larger dialogue on drug quality and would leverage already-existing platforms for greater impact at the policy level. Antihypertensive drugs may even be used as a tracer drug, acting as an
indicator of the larger problem of quality. Approaches to identifying and assessing drug quality should be combined with efforts to strengthen the capacity of developing countries to enforce quality control, registration, and surveillance of drugs that are either imported in or locally manufactured. This could involve adapting approaches from the WHO’s handbook on pharmacovigilance methods, or the US Agency for International Development (USAID)’s Promoting the Quality of Medicines (PQM) program that was designed to ensure the efficacy and quality of medicines for tuberculosis, malaria, and HIV/AIDS. The work to improve quality of antihypertensive drugs should also include continued support of routine surveillance efforts and should go hand in hand with efforts to increase access to these drugs.

3. **Monitor results of ongoing clinical research and support additional clinical and cost-effectiveness research on oral drugs, as needed.**

The study being undertaken by Gynuity Health Projects to compare the efficacy of three commonly used oral antihypertensive drugs (nifedipine, labetalol, and methyldopa) will be pivotal in generating strong evidence needed to support and guide concise recommendations on the oral drugs of choice for HDP. Oral dosage forms would simplify use, and the long-term goal is to identify one oral antihypertensive that can address HDP. The study will also provide valuable information on use of methyldopa for management of acute hypertensive crises in addition to maintenance dosing. Analysis and results are expected by December 2014. The results of the study will be key to:

a. Determining if additional studies are needed, and what these studies would entail to move the agenda forward at the global and national levels. If conclusive, the study could provide the basis for policy formulation and inclusion of specific recommended drugs for HDP on WHO and national EMLs.

b. Development of clear, consistent, evidence-based recommendations for LRS to guide choice of first-line antihypertensive drugs for acute and longer-term blood pressure control during pregnancy and the postpartum period. Specific goals would be to secure the following:

- Consensus around the drugs of choice for treatment and management of acute and severe hypertension in pregnancy.
- Expert global consensus on BP parameters (sBP and dBP) for beginning therapy for moderate and severe hypertension, and for halting therapy during the antenatal and postpartum periods.
- Clear recommendations for managing postpartum hypertension. Hypertension in the postpartum period is not well understood and more evidence is needed to guide the development of clear guidelines for the treatment and management of these women.
- Clear guidelines for acute versus maintenance antihypertensive drug regimens.
- Clear recommendations for the treatment, management, and long-term follow-up of women with HDP complicated by other morbidities, such as cardiovascular disease.

4. **Investigate the novel use of digoxin antibody fragment (DIF) for the treatment of women with severe hypertension and PE.**
A study by Too and Hill\textsuperscript{45} found that women with PE had elevated endogenous digitalis-like factors (EDLF), and the use of DIF reduced BP and improved maternal and neonatal outcomes. Lam et al.\textsuperscript{46} reported on the completion of phase 2 studies of the drug, and preliminary results indicate that DIF stabilized the woman’s condition by neutralizing a key factor associated with PE, in women with severe PE, who were remote from term and who were EDLF-positive. While the study showed that the use of DIF was associated with improved maternal and neonatal outcomes, the results were not conclusive. A large multicenter trial is needed to evaluate the benefits of DIF in women with severe PE after screening them for positive EDLF status.

Development and research on the effectiveness of DIF for the treatment of PE/E should continue to be monitored. DIF, as it is currently available and tested for PE, would be prohibitively expensive for use in LRS. In addition, it requires storage in the cold chain and IV injection, which limit its use to facilities in developing countries with a reliable cold chain and a provider authorized and competent to administer IV injections. If study results indicate that DIF could have a significant impact on PE, a closer look at the cost-effectiveness of the drug might be warranted. PATH has extensive experience working with drug and health technology manufacturers to bring prices down and could engage with the manufacturers of DIF to look for possible ways to make DIF available at lower cost for use in LRS.

5. **Develop clear, consistent, evidence-based recommendations for LRS to guide choice of first-line antihypertensive drugs for acute and longer-term blood pressure control during pregnancy and the postpartum period.** Specific goals would be to secure the following:

a. Expert global consensus on BP parameters (sBP and dBP) for beginning therapy for moderate and severe hypertension, and for halting therapy during the antenatal and postpartum periods.

b. Clear recommendations for managing postpartum hypertension. Hypertension in the postpartum period is not well understood and more evidence is needed to guide the development of clear guidelines for the treatment and management of these women.

c. Clear guidelines for acute versus maintenance antihypertensive drug regimens.

d. Clear recommendations for the treatment, management, and long-term follow-up of women with HDP complicated by other morbidities, such as cardiovascular disease.
References


