Report of the Canadian Hypertension Society Consensus Conference:
3. Pharmacologic treatment of hypertensive disorders in pregnancy

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Abstract

Objective: To provide Canadian physicians with evidence-based guidelines for the pharmacologic treatment of hypertensive disorders in pregnancy.

Options: No medication, or treatment with antihypertensive or anticonvulsant drugs.


Evidence: Pertinent articles published from 1962 to September 1996 retrieved from the Pregnancy and Childbirth Module of the Cochrane Database of Systematic Reviews and from MEDLINE; additional articles retrieved through a manual search of bibliographies; and expert opinion. Recommendations were graded according to levels of evidence.

Values: Maternal and fetal well-being were equally valued, with the belief that treatment side effects should be minimized.

Benefits, harms and costs: Reduction in the rate of adverse perinatal outcomes, including death. Potential side effects of antihypertensive drugs include placental hypoperfusion, intrauterine growth retardation and long-term effects on the infant.

Recommendations: A systolic blood pressure greater than 169 mm Hg or a diastolic pressure greater than 109 mm Hg in a pregnant woman should be considered an emergency and pharmacologic treatment with hydralazine, labetalol or nifedipine started. Otherwise, the thresholds at which to start antihypertensive treatment are a systolic pressure of 140 mm Hg or a diastolic pressure of 90 mm Hg in women with gestational hypertension without proteinuria or pre-existing hypertension before 28 weeks’ gestation, those with gestational hypertension and proteinuria or symptoms at any time during the pregnancy, those with pre-existing hypertension and underlying conditions or target-organ damage, and those with pre-existing hypertension and superimposed gestational hypertension. The thresholds in other circumstances are a systolic pressure of 150 mm Hg or a diastolic pressure of 95 mm Hg. For nonsevere hypertension, methyldopa is the first-line drug; labetalol, pindolol, oxprenolol and nifedipine are second-line drugs. Fetal distress attributed to placental hypoperfusion is rare, and long-term effects on the infant are unknown. Magnesium sulfate is recommended for the prevention and treatment of seizures.

Validation: The guidelines are more precise but compatible with those from the US and Australia.

Sponsor: Preparation of the guidelines was funded by the Canadian Hypertension Society. The guidelines are endorsed by the Canadian Hypertension Society, the Society of Obstetricians and Gynaecologists of Canada and the Association of obstétriciens-gynécologues du Québec.

Résumé

Objectif: Formuler des lignes directrices définitives à l’intention des médecins canadiens qui fournissent des soins prénataux pour le traitement pharmacologique des problèmes hypertensifs de la grossesse.

Option: Aucun médicament ou traitement aux agents hypotenseurs ou anticonvulsivants.
Hypertensive disorders in pregnancy pose serious risks for both mother and fetus. The pharmacologic treatment of them is a medical and obstetric challenge. There are currently no uniform guidelines in Canada for the management of hypertension in pregnancy because of a lack of good information about whether pharmacologic intervention is necessary and how to initiate it. This article provides evidence-based guidelines for Canadian physicians who provide care to pregnant women. Although US and Australian guidelines exist, ones specific to Canada are necessary because populations and health care systems are different.

**Methods**

The details of the consensus process are provided in part 1 of the series. In brief, the Canadian Hypertension Society (CHS) decided in 1994 to develop a Canadian consensus on the diagnosis and management of hyperten-
Pharmacologic treatment of hypertension in pregnancy

The president of the society and cochair were charged to create panels to address the 3 parts of the project: definitions, evaluation and classification; nonpharmacologic management and prevention; and pharmacologic treatment.

The members of the panel addressing pharmacologic treatment were chosen for their expertise in obstetrics, internal medicine and clinical pharmacology. The work was distributed among the members, and one of them (E.R.) reviewed the literature and the prepared information. The panel members reviewed available evidence published from 1962 to September 1996 retrieved from various sources: articles retrieved through a MEDLINE search (English and French literature) using the terms “human pregnancy toxemia,” “pre-eclampsia,” “eclampsia,” “complications [cardiovascular]” and “hypertension”; the bibliographies of retrieved reports, review articles and personal files of panel members; and the Pregnancy and Childbirth Module of the Cochrane Database of Systematic Reviews. The levels of evidence were graded according to the methods of critical appraisal of research papers described by Sackett, and the recommendations were graded according to the level of evidence supporting them (Appendix 1).

The chair and cochair of the CHS at the time of the consensus project (Simon W. Rakbin and Robert F. Burrows) were involved as external reviewers. The initial recommendations were carried forward if approved by all of the panel members or were reached by a collective vote. In some areas, evidence-based recommendations were impossible, and therefore the opinions of experts were presented. The members of the panel revised the draft report several times. The final version of the recommendations, presented at a general consensus conference in Montreal in 1995, was endorsed by the CHS, the Society of Obstetricians and Gynaecologists of Canada and the Association des obstétriciens-gynécologues du Québec.

Because the focus of pharmacologic treatment of hypertension in pregnancy should be on decreasing maternal and neonatal morbidity and mortality, the primary outcomes of interest were defined as follows: in cases of nonsevere hypertension, perinatal death (including death late in the second trimester), severe hypertension, superimposed gestational hypertension, preterm delivery and intrauterine growth retardation (IUGR); in cases of severe hypertension, perinatal death and preterm delivery; and in cases for which anticonvulsant therapy is required, seizures and perinatal death. Because these outcomes were not available from all trials reviewed, they were equally ranked. Despite the obvious importance of maternal death, there was insufficient data to include it as a primary outcome. The efficacy of a drug in decreasing blood pressure was defined as an intermediate outcome.

Hypertensive disorders in pregnancy were classified as pre-existing hypertension, gestational hypertension (with or without proteinuria) and unclassified hypertension, as defined in part 1 of the series. Because there was no specific study on gestational hypertension superimposed on pre-existing hypertension, recommendations for gestational hypertension apply for this disorder.

The use of pharmacologic treatment does not exclude the use of nonpharmacologic therapy, reported in part 2.

Deciding on when to treat

The recommendations on deciding when to treat hypertensive disorders in pregnancy are presented in Table 1.

There is general agreement that pregnant women with a systolic blood pressure greater than 169 mm Hg or a diastolic pressure greater than 109 mm Hg, or both, should receive pharmacologic treatment to prevent maternal intracerebral hemorrhage. For lower readings, there was lack of consensus in the literature on what is appropriate management. There was no report that specifically addressed the critical blood pressure at which pharmacologic treatment should be initiated for the prevention of perinatal death and maternal complications.

Incidence rates of perinatal death and IUGR increase with elevation in blood pressure, with or without proteinuria. An observational study involving 12 954 American women from 1959 to 1967 revealed that neonatal mortality increased when the mean arterial pressure was more than 89 mm Hg in the second trimester and more than 104 mm Hg in the third trimester. (The mean arterial pressure is calculated as [systolic + (2 × diastolic)] ÷ 3; for example, a blood pressure of 120/75 mm Hg would give a mean arterial pressure of 90 and a blood pressure of 142/85 mm Hg would give a mean arterial pressure of 104 mm Hg.) In another cohort of 50 806 American women, a diastolic blood pressure of 95 mm Hg in the absence of proteinuria and 85 mm Hg with proteinuria after 28 weeks’ gestation was observed to be the threshold for an increase in the rate of perinatal death. In cases of pre-existing hypertension, a diastolic blood pressure greater than 100 mm Hg before 20 weeks’ gestation, left ventricular hypertrophy and a serum creatinine level of more than 88.4 µmol/L are risk factors for superimposed gestational hypertension and IUGR. In a randomized controlled trial (RCT) of the effectiveness of methyldopa in decreasing perinatal mortality, the blood pressures used to include women in the study were 140/90 mm Hg before 28 weeks’ gestation and 150/95 mm Hg thereafter. In cases of nonsevere gestational hypertension, most of the RCTs reviewed had a criterion of 140/90 mm Hg as the blood pressure for inclusion. Thus, from the little data available, it appears that different thresholds could be used depending on the presence of proteinuria and the gestational age.
No data were found to determine the optimal blood pressure to be attained with antihypertensive treatment. When specified in the trials, the aim of the treatment was to lower diastolic blood pressure to below 90 mm Hg. The uncertainty is aggravated by the fact that there were no human data available on the autoregulation of the uteroplacental circulation. Antihypertensive drugs (when used at recommended dosages) do not seem to alter placental and fetal Doppler wave forms, which are used experimentally as a method to study uteroplacental vascular impedance.

There is no established blood pressure threshold on which pharmacologic treatment may be started based on self-monitoring and automated 24-hour ambulatory monitoring.

**Treatment of nonsevere hypertension**

The recommendations about the treatment of nonsevere hypertension (blood pressure less than 170/110 mm Hg) are presented in Table 2 and Appendix 2.

There were few RCTs on the efficacy of different pharmacologic interventions for the treatment of nonsevere hypertension. Studies involving women with pre-existing hypertension in the first trimester were rare because blood pressure normally decreases in the first half of pregnancy. In gestational hypertension the effects of the drugs are time-limited, because delivery is considered the ultimate treatment of this disorder. The more frequent methodological problems were the inclusion of a heterogeneous population (which made it difficult to distinguish between pre-existing and gestational hypertension), the use of 2 drugs in the protocol, and the exclusion of an important number of women from the final analysis (which raises a concern about the potential for bias).

**Effect on maternal and perinatal outcomes**

**Perinatal death**

Perinatal death is rare. The only 2 RCTs reporting a

| Table 2: Recommended treatment of nonsevere hypertension in pregnancy |
|-------------------------|------------------|
| **Treatment goal**       | DBP 80–90 mm Hg (grade D) |
| **First-line drug**      | Methyldopa (grade A/B) |
| **Second-line drugs**    | Labetalol (grade A/B), Clonidine (grade A/B/C) |
| **Third-line drugs**     | Nifedipine (grade A/B/C), Atenolol (grade A/B/C) |
| **Special indications**  | Nifedipine + hydralazine (grade E) |
| **Drugs to avoid**       | Angiotensin-converting enzyme inhibitors, Angiotensin II receptor antagonists |

*These recommendations do not apply to women in labour. See Appendix 1 for definitions of the grades of recommendations. DBP = diastolic blood pressure.
Pharmacologic treatment of hypertension in pregnancy

December 1997; 157(9):1249-1259

Pharmacologic treatment of hypertension in pregnancy

December 1997; 157(9):1249-1259

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Pharmacologic treatment of hypertension in pregnancy
Fetal and neonatal \( \beta \)-blockage: Decreased blood pressure or heart rate, or both, in the fetus and the newborn were reported with the use of acetazolam, atenolol and metoprolol.\(^{12,26,28}\)

Long-term infant development: Methyldopa was the only drug for which a longitudinal study, with a follow-up period of 7.5 years, showed adequate development of children exposed in utero.\(^{29}\) Studies of the long-term safety of atenolol and labetalol were small and limited to follow-up periods of 1 year and 6 months after birth.\(^{80,81}\) Data did not exist for other antihypertensive drugs.

Interaction with magnesium sulfate: A possible increase in the hypotensive effect of nifedipine and neuromuscular \( \beta \)-blockage were reported when nifedipine and magnesium sulfate were used concomitantly.\(^{42,45}\)

Other drugs: There were insufficient data on prazosin, nicardipine, verapamil, isradipine and nisoldipine (currently not available in Canada) to provide reliable information on their efficacy and safety.

**Treatment of severe hypertension**

The recommendations about the treatment of severe hypertension are presented in Table 3 and Appendix 2.

The definition of severe hypertension in pregnancy differs from that used for nonpregnant individuals. In nonpregnant people, severe hypertension is usually defined as a diastolic blood pressure greater than 115–120 mm Hg. In pregnant women, severe hypertension is usually defined as a systolic blood pressure greater than 160 or 169 mm Hg or a diastolic blood pressure greater than 109 mm Hg, or both. These levels are chosen because a diastolic pressure of more than 109 mm Hg is associated with cerebral hemorrhage.\(^{4,5}\)

There were no placebo-controlled trials examining the effect of treatment of severe hypertension in pregnant women, and none will likely be performed because of ethical considerations. It is accepted that, because the significant elevation of blood pressure is associated with poor outcome, treatment is necessary during pregnancy or postpartum if the blood pressure is 170/110 mm Hg or higher.

There were few RCTs comparing the effectiveness of 2 drugs in preventing adverse outcomes that would validate the clinical impressions.\(^{90,91,92}\) The samples were too small and inadequate to meet the criteria for level I evidence.

Methyldopa, hydralazine, labetalol and nifedipine were found to be effective in decreasing blood pressure in cases of severe hypertension (level II evidence).\(^{92,93,94}\) Labetalol and nifedipine were also useful in decreasing the pressor response to tracheal intubation (level II evidence).\(^{95,96}\) Fetal distress attributed to placental hypoperfusion was reported in some cases, usually when high doses were used, the blood pressure decreased rapidly or the goal diastolic pressure was too low.\(^{72,75}\) Concomitant use of nifedipine and magnesium sulfate was shown to cause severe hypotension and fetal distress.\(^{72,78}\) Placental hypoperfusion was not observed with sublingual use of nifedipine, but experience was limited.\(^{72,79}\) Hydralazine and nifedipine may induce maternal tachycardia, which may limit their efficacy.

Diazoxide, even in low doses, was associated with significant hypotension, arrested labour\(^{97}\) and maternal and neonatal hyperglycaemia.\(^{73,75}\) Sodium nitroprusside was shown to be effective in cases of severe hypertension, but its use was infrequent.\(^{79,80}\) Brief infusions of low-dose sodium nitroprusside were not found to result in toxic fetal cyanide levels in small observational studies.\(^{70,80}\)

### Table 3: Recommended treatment of severe hypertension in pregnancy

<table>
<thead>
<tr>
<th>Treatment goal</th>
<th>DBP 90–100 mm Hg (grade D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line drugs</td>
<td>Labetalol (grade B)(^{15,16})</td>
</tr>
<tr>
<td></td>
<td>Nifedipine (grade B)(^{17,18})</td>
</tr>
<tr>
<td>Special indications</td>
<td>Diazoxide (grade D)</td>
</tr>
<tr>
<td></td>
<td>Sodium nitroprusside (grade D)</td>
</tr>
<tr>
<td>Caution</td>
<td>Neurornuscular function and blood pressure should be closely monitored when using nifedipine + magnesium sulfate (grade D)</td>
</tr>
<tr>
<td></td>
<td>Fetal heart rate should be monitored during acute treatment (grade D)</td>
</tr>
</tbody>
</table>

### Table 4: Recommended treatment of postpartum hypertension

<table>
<thead>
<tr>
<th>Indication</th>
<th>Treatment goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe hypertension (Table 3)</td>
<td>DBP &gt; 99 mm Hg 3 days after delivery and target-organ damage (grade D)</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>Methyldopa (grade B)(^{81,82})</td>
</tr>
<tr>
<td></td>
<td>Nifedipine (grade B)(^{83})</td>
</tr>
<tr>
<td></td>
<td>Timolol (grade B)(^{84})</td>
</tr>
</tbody>
</table>

### Table 5: Recommended treatment with anticonvulsant drugs

<table>
<thead>
<tr>
<th>Indication</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis for hypertension-related seizures: no data available to recommend when it should be used</td>
<td>Magnesium sulfate (grade A)(^{85})</td>
</tr>
<tr>
<td>Therapy for hypertension-related seizures (grade A)(^{86})</td>
<td>Magnesium sulfate (grade A)(^{85})</td>
</tr>
</tbody>
</table>
tational hypertension will often have a spontaneous decrease in blood pressure after delivery. Women with severe hypertension are usually managed as described previously. Methyldopa, timolol and nifedipine were studied for their use in the postpartum period and were found to be effective in decreasing blood pressure (level II evidence).81–83 These drugs are excreted in breast milk. No adverse effects were reported in nursing infants, but long-term exposure to these drugs has not been studied. These antihypertensive drugs are considered as being compatible with breast feeding by the American Academy of Pediatrics.84

**Anticonvulsant therapy**

The recommendations about anticonvulsant drug therapy are in Table 5. Anticonvulsant drugs are used to prevent seizures and the recurrence of seizures in women with hypertensive disorders. Thus, the relevant clinical outcomes are the incidence of seizures and perinatal death. For both outcomes, there were few RCTs available, and except for 2 recent reports the number of women involved was small.85–90

Hypertension-related seizures are rare, and are more frequent in developing countries.91,92 In a study in Hamilton, Ont., 1.4% of women with hypertensive disorders had seizures without preventive anticonvulsant therapy:93 0.6% of those with pre-existing hypertension, 0.1% with gestational hypertension without proteinuria, 4.3% with gestational hypertension with proteinuria, and 2.1% with superimposed gestational hypertension with proteinuria.

In the literature, prophylactic anticonvulsant therapy was recommended in all women with elevated blood pressure46 or in those with gestational hypertension55 or severe hypertension,66 without firm data to support any of these statements.

We found 3 RCTs comparing magnesium sulfate and phenytoin in the prevention of hypertension-related seizures.67–69 In 2 of them, involving women with severe gestational hypertension, no convulsions or perinatal deaths were reported in the treatment groups (level II evidence).67,68 The third study involved 3534 hypertensive women treated either with magnesium sulfate (intramuscularly) or phenytoin (by intravenous bolus, then orally).69 Seizures were reported to occur less frequently in the magnesium sulfate group (level I evidence); the incidence of perinatal deaths was similar in the 2 groups (level II evidence). However, this study used an extremely liberal approach to anticonvulsant therapy: it was given to all women with a blood pressure greater than 140/90 mm Hg. Eighteen percent of the study population had a result of +2 on a proteinuria dipstick test, and 4% received antihypertensive drug therapy. It is difficult to generalize the results of this study to Canadian practice.

Magnesium sulfate, phenytoin and diazepam have been studied in women with hypertension-related seizures.65,86,90 The larger trial, a multicentre randomized study, involved 1680 women. In one group, magnesium sulfate was compared with phenytoin, and in another group it was com-

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**Table 6: Recommendations related to treatment of hypertension and seizures in pregnancy issued by the Canadian Hypertension Society (CHS) and other international bodies**

<table>
<thead>
<tr>
<th>Category</th>
<th>CHS</th>
<th>NHBPEPWG99</th>
<th>ASSH100</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonsevere</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP readings at which to start treatment, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP &gt; 119 or 149 or DBP &gt; 89 or 94</td>
<td>DBP &gt; 99</td>
<td>DBP &gt; 159 or DBP &gt; 89</td>
<td></td>
</tr>
<tr>
<td>Treatment goal, mm Hg</td>
<td>DBP 80-90</td>
<td>–</td>
<td>DBP &gt; 110</td>
</tr>
<tr>
<td>Drugs</td>
<td>Methyldopa, labetalol, pindolol, oxprenolol, nifedipine</td>
<td>Methyldopa</td>
<td>Methyldopa, labetalol, oxprenolol, clonidine</td>
</tr>
<tr>
<td>Drugs to avoid</td>
<td>ACE inhibitors, angiotensin II receptor antagonists</td>
<td>ACE inhibitors</td>
<td>ACE inhibitors, diuretics</td>
</tr>
<tr>
<td><strong>Severe</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP readings at which to start treatment, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP &gt; 169 or DBP &gt; 109</td>
<td>DBP &gt; 104</td>
<td>DBP &gt; 169 or DBP &gt; 114</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>Hydralazine, labetalol, nifedipine</td>
<td>Hydralazine</td>
<td>Hydralazine, labetalol nifedipine, diazoxide</td>
</tr>
<tr>
<td>Drugs for prophylaxis</td>
<td>Magnesium sulfate</td>
<td>Magnesium sulfate</td>
<td>Magnesium sulfate, phenytoin</td>
</tr>
<tr>
<td>Drugs for treatment</td>
<td>Magnesium sulfate</td>
<td>Magnesium sulfate</td>
<td>Diazepam intravenously</td>
</tr>
</tbody>
</table>

*NHBPEPWG = National High Blood Pressure Education Program Working Group (US); ASSH = Australasian Society for Study of Hypertension.†ACE = angiotensin-converting enzyme.
pared with diazepam.80 The women receiving the magnesium sulfate had a 52% lower risk of recurrent seizures than those receiving diazepam and a 67% lower risk than those receiving phenytoin (level I evidence); all 3 groups had similar rates of perinatal death (level II evidence).

Major maternal side effects of magnesium sulfate and phenytoin are unusual, and the rate of withdrawal is similar.81 A number of minor adverse effects are attributed to the 2 drugs: for example, hot flushes and dyspnea with magnesium sulfate and transient burning at the intravenous site and ataxia with phenytoin. The major side effects of magnesium sulfate (respiratory depression and heart block) are due to overdose or renal insufficiency. Magnesium sulfate may cause hypotension or neuromuscular blockage when used with nifedipine or in women with myoneuronal disorders.62–65 There have been no adverse neonatal effects documented with the short-term use of phenytoin. Magnesium sulfate may decrease short- and long-term fetal heart rate variability.86

Validation

The panel members reviewed the US and Australian consensus statements.80,86 Certain discrepancies exist between the 2 statements (Table 6). Some of them are explained by the fact that the Australian recommendations were published later and based on data not available to the US group. In the Australian report, pharmacologic treatment of gestational hypertension is favoured because of the relative safety of the drugs and the potential benefit of reducing the risk of premature delivery. Our recommendations concerning the blood pressures at which to start treatment are more precise than those of the US and Australian panels, because we have taken into account the kind of hypertensive disorder and the gestational age as well as the presence of proteinuria and symptoms. As for the recommendations concerning which drugs to use, our recommendations are consistent with the US and Australian ones.

We thank Drs. Simon W. Rabkin and Robert F. Burrows for reviewing an earlier draft of the manuscript. The consensus project was funded by the Canadian Hypertension Society. The society gratefully acknowledges the receipt of a grant worth $50000 from Roberts Pharmaceutical Canada Inc. to help defray meeting costs associated with initiating the consensus project.

References


Pharmacologic treatment of hypertension in pregnancy


### Appendix 1: Levels of evidence used to rate studies of the treatment of hypertensive disorders in pregnancy and to grade recommendations

<table>
<thead>
<tr>
<th>Levels of evidence</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Randomized controlled trial (RCT) that demonstrates statistically significant difference in at least 1 important outcome (e.g., survival or major illness)</td>
</tr>
<tr>
<td>II</td>
<td>RCT that does not meet the level I criteria</td>
</tr>
<tr>
<td>III</td>
<td>Observational study (e.g., retrospective case series)</td>
</tr>
<tr>
<td>IV</td>
<td>Case series (at least 10 patients) without control subjects</td>
</tr>
<tr>
<td>V</td>
<td>Case report (less than 10 patients)</td>
</tr>
</tbody>
</table>

### Appendix 2: Recommended dosages of antihypertensive drugs (grade D)

<table>
<thead>
<tr>
<th>Condition; drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsevere hypertension</td>
<td></td>
</tr>
<tr>
<td>Methyldopa</td>
<td>500 mg bid-qid</td>
</tr>
<tr>
<td>Labetalol</td>
<td>200-600 mg bid-tid</td>
</tr>
<tr>
<td>Oxytetracynol</td>
<td>20-80 mg bid-tid</td>
</tr>
<tr>
<td>Pindolol</td>
<td>5-15 mg bid</td>
</tr>
<tr>
<td>Nitrendipine</td>
<td>20-40 mg of long-acting formulation (PA) bid</td>
</tr>
<tr>
<td>Clonidine</td>
<td>0.5-2.0 mg bid-qid</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>10-50 mg bid-qid</td>
</tr>
<tr>
<td>Severe hypertension</td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>5-10 mg intravenously IV q 20 min or infusion of 0.5-10 mg/h</td>
</tr>
<tr>
<td>Labetalol</td>
<td>10-20 mg IV q 10 min up to 300 mg or infusion of 1-2 mg/min</td>
</tr>
<tr>
<td>Nitrendipine</td>
<td>10 mg orally q 2-3 h</td>
</tr>
</tbody>
</table>


### Graduation system for recommendations

<table>
<thead>
<tr>
<th>Graduation system</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>The recommendation is based on 1 or more studies at level I</td>
</tr>
<tr>
<td>B</td>
<td>The best evidence available was at level II</td>
</tr>
<tr>
<td>C</td>
<td>The best evidence available was at level III</td>
</tr>
<tr>
<td>D</td>
<td>The best evidence available was lower than level III and included exported opinion</td>
</tr>
</tbody>
</table>