

What is the ideal antihypertensive agent for pre-eclampsia/eclampsia?

Peter von Dadelszen

MBChB, DPhil, FRANZCOG, FRCSC, FRCOG

Associate Professor of Obstetrics & Gynaecology, UBC

Consultant in Maternal-Fetal Medicine, BC Women's

Co-Director, CFRI Reproduction & Healthy Pregnancy Cluster

Why use antihypertensives?

- Maternal stroke risk associated with both severe systolic and/or diastolic hypertension

- sBP >160mmHg

- dBP >110mmHg

CEMACH 2007

- Severe hypertension associated with placental abruption and attendant maternal and perinatal risks
- Severe hypertension is included in most definitions of 'severe' pre-eclampsia, although such classification systems are flawed

Menzies et al. Hypertens Pregnancy 2007

Why use antihypertensives?

- **In non-severe pregnancy hypertension**
 - **No clear evidence of benefit other than to reduce the frequency of episodes of severe hypertension**
 - **May adversely effect fetal growth velocity**

von Dadelszen *et al.* *Lancet* 2000

- **Therefore, my focus will be on the pharmacological management of severe hypertension**

The 'ideal' agent in rural & remote settings

- Oral administration
- Reliable reduction in BP
- Smooth reduction in BP
- Rapid onset of action
- Minimal overshoot
 - **BP in target range**
 - sBP 130-160mmHg
 - dBP 80-110mmHg
- Preferential CNS vascular effect
- No maternal or fetal toxicity

From what can we choose?

- Hydralazine
- Beta-blockers (& alpha-/beta-blockers)
 - Labetalol
- Calcium channel blockers
 - Nifedipine
- Alpha-methyldopa
- Angiotensin converting enzyme inhibitors
- Angiotensin-II receptor blockers

The 'ideal' agent in rural & remote settings

- Oral administration
- Reliable reduction in BP
- Smooth reduction in BP
- Rapid onset of action
- Minimal overshoot
 - BP in target range
 - sBP 130-160mmHg
 - dBP 80-110mmHg
- Preferential CNS vascular effect
- **No maternal or fetal toxicity**

From what can we choose?

- Hydralazine
- Beta-blockers (& alpha-/beta-blockers)
 - Labetalol
- Calcium channel blockers
 - Nifedipine
- Alpha-methyldopa
- Angiotensin converting enzyme inhibitors
- Angiotensin-II receptor blockers

From what can we choose?

- Hydralazine
- Beta-blockers (& alpha-/beta-blockers)
 - Labetalol
- Calcium channel blockers
 - Nifedipine
- Alpha-methyldopa
- ~~Angiotensin converting enzyme inhibitors~~
- ~~Angiotensin-II receptor blockers~~
 - Risks of fetal renal toxicity and IUFD

From what can we choose?

- **MgSO₄ is NOT an antihypertensive**

The 'ideal' agent in rural & remote settings

- **Oral administration**
- Reliable reduction in BP
- Smooth reduction in BP
- Rapid onset of action
- Minimal overshoot
 - BP in target range
 - sBP 130-160mmHg
 - dBP 80-110mmHg
- Preferential CNS vascular effect
- No maternal or fetal toxicity

Oral administration

- Labetalol
- Nifedipine capsules
- Nifedipine intermediate acting
 - PA/Retard
- Hydralazine

Magee & Abdullah. *Expert Opin Drug Saf* 2004

The 'ideal' agent in rural & remote settings

- Oral administration
- **Reliable reduction in BP**
- Smooth reduction in BP
- Rapid onset of action
- Minimal overshoot
 - BP in target range
 - sBP 130-160mmHg
 - dBP 80-110mmHg
- Preferential CNS vascular effect
- No maternal or fetal toxicity

Reliable reduction in BP severe hypertension

- CCBs are more reliable than hydralazine in lowering BP in pregnant women with severe hypertension

Magee et al. BMJ 2004

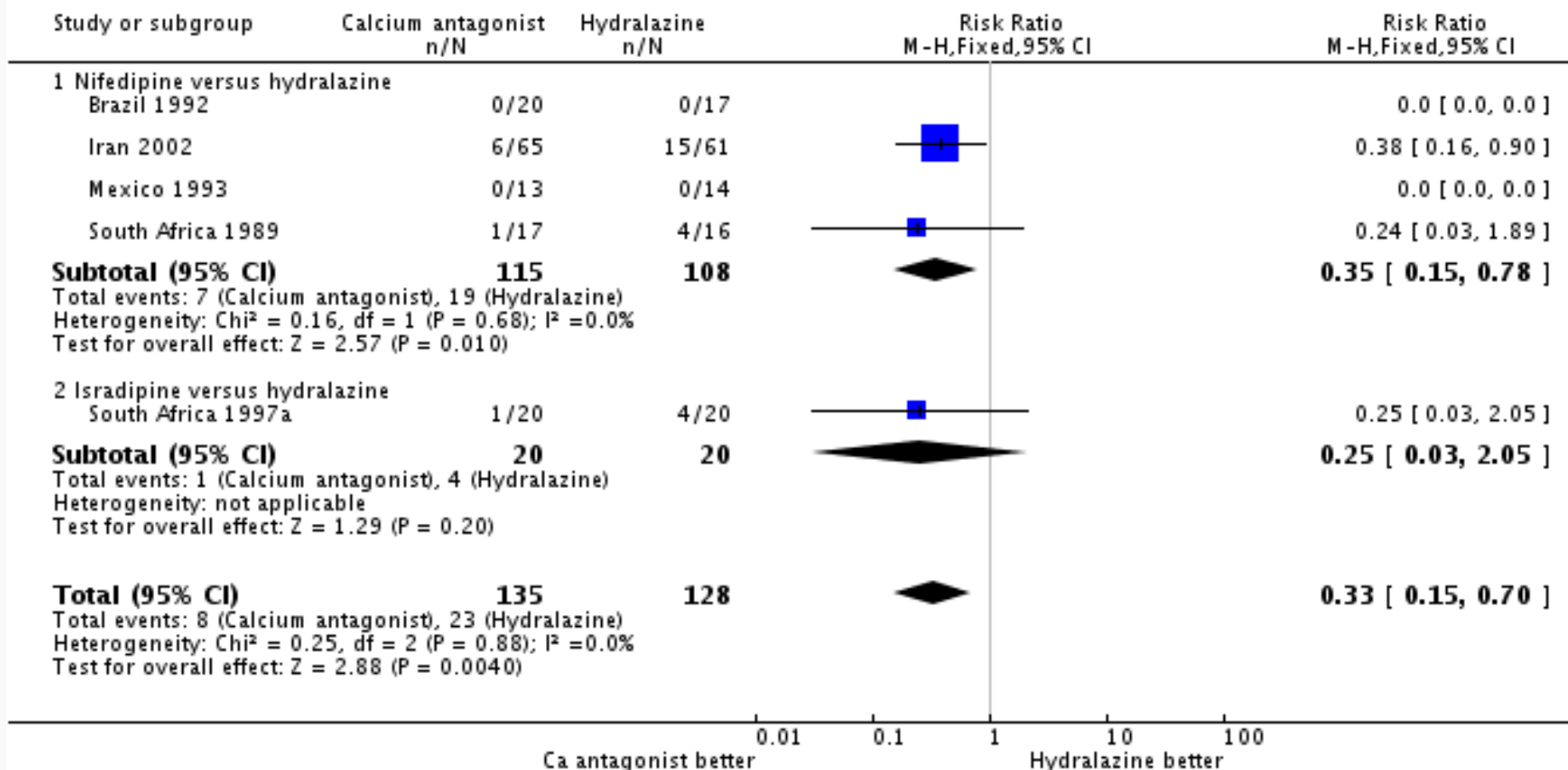
Duley et al. CDSR 2006

- Hydralazine appears more reliable than labetalol

Magee et al. BMJ 2004

- Black women's BP tends to be beta-blocker resistant
- Methyldopa is not an agent of choice for severe hypertension
 - Onset of action over 2-3 days
 - No evidence that loading dose effective

Review: Drugs for treatment of very high blood pressure during pregnancy
 Comparison: 2 Calcium channel blockers versus hydralazine
 Outcome: 1 Persistent high blood pressure



Reliable reduction in BP severe hypertension

- CCBs are more reliable than hydralazine in lowering BP in pregnant women with severe hypertension

Magee et al. BMJ 2004

Duley et al. CDSR 2006

- **Hydralazine appears more reliable than labetalol**

Magee et al. BMJ 2004

- Black women's BP tends to be beta-blocker resistant
- Methyldopa is not an agent of choice for severe hypertension
 - Onset of action over 2-3 days
 - No evidence that loading dose effective

Hydralazine v labetalol

Ashe ⁴¹	2/10	6/10		10.3	0.33 (0.09 to 1.27)
Bhorat ⁴²	0/16	0/18		0.0	Not estimable
Garden ⁴⁴	0/6	0/6		0.0	Not estimable
Mabie ⁴⁷	0/20	4/40		5.2	0.22 (0.01 to 3.84)
Subtotal (95% CI)	2/52	10/74		15.5	0.29 (0.08 to 1.04)

Test for heterogeneity: $\chi^2=0.08$, $df=1$, $P=0.78$

Test for overall effect: $z=-1.91$, $P=0.06$

Total (95% CI)	60/346	30/383		100.0	1.08 (0.78 to 1.49)
----------------	--------	--------	--	-------	---------------------

Test for heterogeneity: $\chi^2=28.09$, $df=9$, $P=0.0009$

Test for overall effect: $z=0.47$, $P=0.6$

0.001 0.02 1 50 1000

Favours
hydralazine

Favours
other
antihypertensives

Fig 1 Persistent severe maternal hypertension in trials that compared hydralazine with other antihypertensives

Reliable reduction in BP severe hypertension

- CCBs are more reliable than hydralazine in lowering BP in pregnant women with severe hypertension

Magee et al. BMJ 2004

Duley et al. CDSR 2006

- Hydralazine appears more reliable than labetalol

Magee et al. BMJ 2004

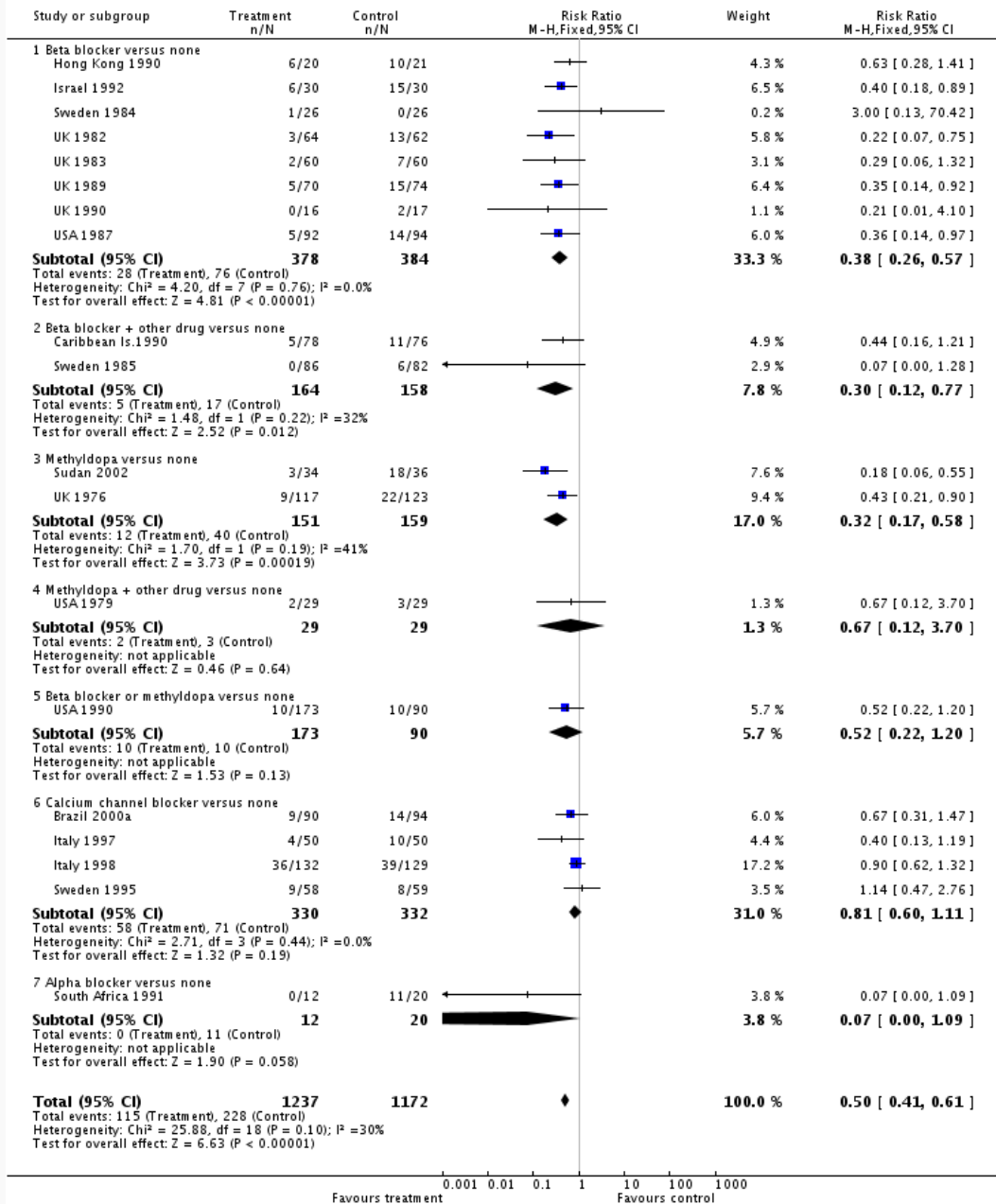
- **Black women's BP tends to be beta-blocker resistant**
- **Methyldopa is not an agent of choice for severe hypertension**
 - **Onset of action over 2-3 days**
 - **No evidence that loading dose effective**

Reliable reduction in BP non-severe hypertension

- **Antihypertensive use in women with non-severe pregnancy hypertension reduces the risk of developing severe hypertension**
- **Effect is consistent across drug classes**
- **Effect significant for beta-blockers alone due to number of RCTs and total number of women enrolled**

Abalos et al. CDSR 2007

Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy
 Comparison: 1 Any antihypertensive drug versus none (subgrouped by class of drug)
 Outcome: 3 Severe hypertension



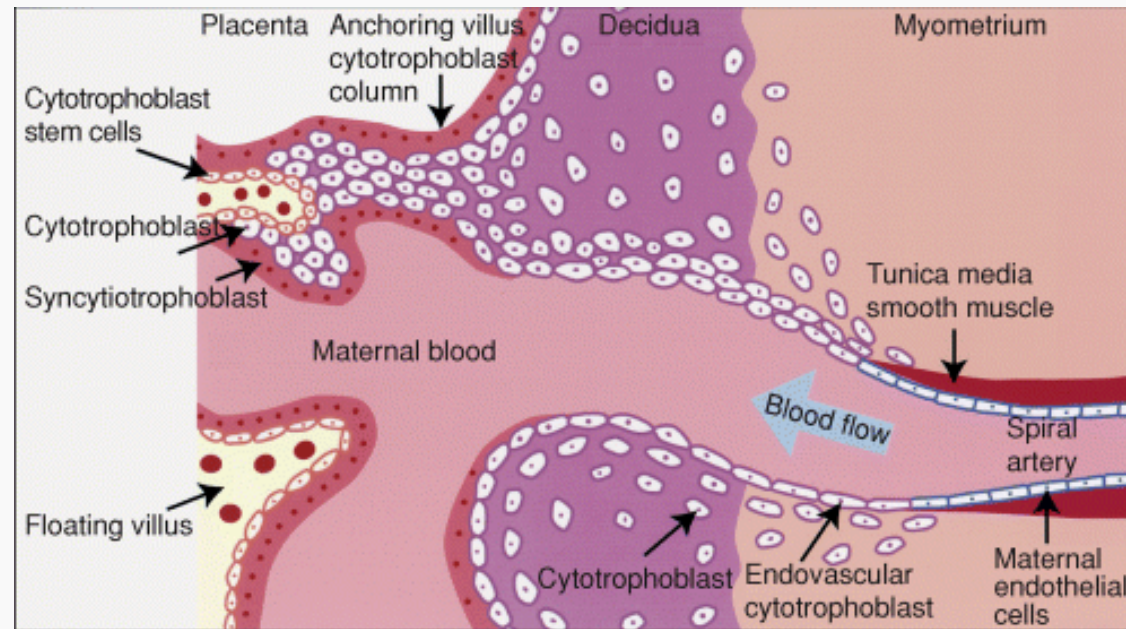
The 'ideal' agent in rural & remote settings

- Oral administration
- Reliable reduction in BP
- **Smooth reduction in BP**
- Rapid onset of action
- Minimal overshoot
 - BP in target range
 - sBP 130-160mmHg
 - dBP 80-110mmHg
- Preferential CNS vascular effect
- No maternal or fetal toxicity

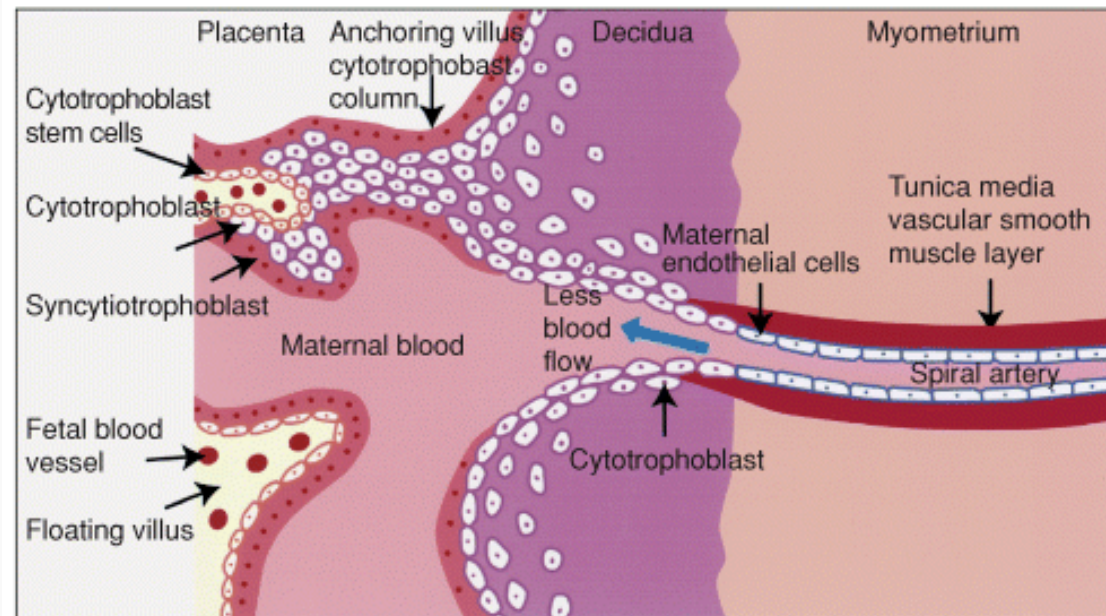
Smooth reduction in BP

- The ideal agent will reduce BP effectively and over a relatively short period of time
 - <60min
 - Stabilise and reduce MAP by 10% per hour
- BP fall will not be precipitous
 - Adverse maternal CNS effects
 - Adverse fetal effects

Normal Pregnancy



Early-onset pre-eclampsia



The 'ideal' agent in rural & remote settings

- Oral administration
- Reliable reduction in BP
- Smooth reduction in BP
- **Rapid onset of action**
- Minimal overshoot
 - BP in target range
 - sBP 130-160mmHg
 - dBP 80-110mmHg
- Preferential CNS vascular effect
- No maternal or fetal toxicity

'Rapid' onset of action

- **Nifedipine capsules**
 - 10-15 min
- **Nifedipine PA/Retard**
 - 30-45 min
- **Labetalol (oral)**
 - 30-45 min

Magee & Abdullah. *Expert Opin Drug Saf* 2004

The 'ideal' agent in rural & remote settings

- Oral administration
- Reliable reduction in BP
- Smooth reduction in BP
- Rapid onset of action
- **Minimal overshoot**
 - **BP in target range**
 - sBP 130-160mmHg
 - dBP 80-110mmHg
- Preferential CNS vascular effect
- No maternal or fetal toxicity

Minimal overshoot

- **CCBs less likely to cause overshoot than hydralazine** *Magee et al. BMJ 2004*
- **Beta-blockers less likely to cause overshoot than hydralazine** *Magee et al. BMJ 2004*
- **Nifedipine PA/Retard less likely to cause overshoot than capsules?** *Brown et al. AJOG 2002*
 - **Small RCT**
 - **End-point ('in range BP') measured at time PA approaching maximal effect**

Minimal overshoot

- **Institutional experience with nifedipine PA**
 - **Environment used to capsules**
 - **Clinical misunderstanding of the formulations**
 - **Overdosing with PA tablets as clinicians anticipate rapid onset of action**
 - **Up to 3 doses before 1st dose effective**

The 'ideal' agent in rural & remote settings

- Oral administration
- Reliable reduction in BP
- Smooth reduction in BP
- Rapid onset of action
- Minimal overshoot
 - BP in target range
 - sBP 130-160mmHg
 - dBP 80-110mmHg
- **Preferential CNS vascular effect**
- No maternal or fetal toxicity

Preferential CNS vascular effect

- **Some evidence to support labetalol as being a particular CNS vascular stabiliser**
- **Role in seizure prophylaxis?**
- **LIMPET**

Belfort et al. Obstet Gynecol Surv 2006

The 'ideal' agent in rural & remote settings

- Oral administration
- Reliable reduction in BP
- Smooth reduction in BP
- Rapid onset of action
- Minimal overshoot
 - BP in target range
 - sBP 130-160mmHg
 - dBP 80-110mmHg
- Preferential CNS vascular effect
- **No maternal or fetal toxicity**

No maternal toxicity

- **Nifedipine**

- **Historical concern about interaction with MgSO₄**

- No evidence of risk

Magee et al. AJOG 2005

- **Capsules, reflex tachycardia, and cardiac events**

- Risks limited to women

- >45yo

- DbM >15y

- Known IHD

- Aortic stenosis

- **Labetalol**

- **Hepatitis**

- HELLP mimicker

The 'ideal' agent in rural & remote settings

- Oral administration
- Reliable reduction in BP
- Smooth reduction in BP
- Rapid onset of action
- Minimal overshoot
 - BP in target range
 - sBP 130-160mmHg
 - dBP 80-110mmHg
- Preferential CNS vascular effect
- No maternal or fetal toxicity

On balance

- **The intervention package should include one/two oral antihypertensive agent(s)**
- **The choice for a single antihypertensive lies between nifedipine and labetalol**
- **Theoretical and practical reasons to have both available**
 - **Combination beta-blockade and vasodilatation**
 - **Second effective agent for women whose BP is resistant to one or other agent**