What's new in hypertension management during pregnancy

NASOM & GÉMOQ Conference 2023

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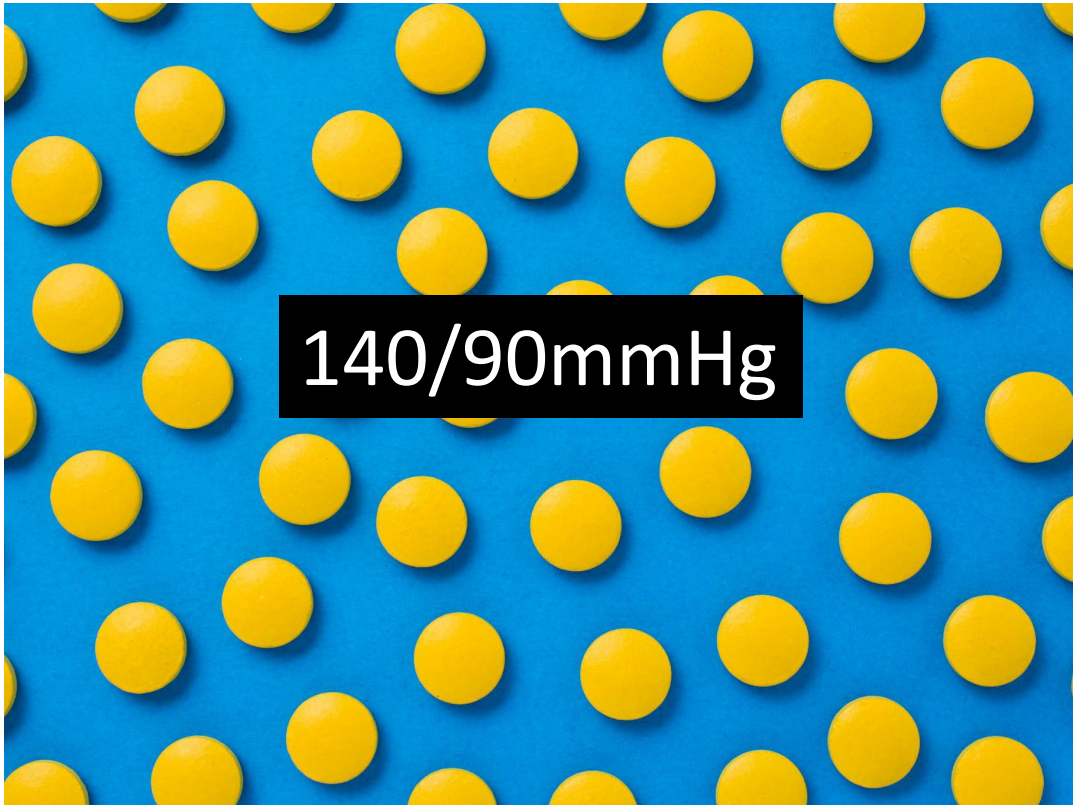
(No relevant disclosures)

Main points

- Treat hypertension from a 140/90mmHg threshold
- For severe hypertension, trend towards use of oral agents
- For non-severe hypertension, antihypertensives titrated to a target diastolic BP of 85mmHg are better for mother without increasing risk to baby
- While there is a wide choice of antihypertensive agents, labetalol may have some advantages over others
- When necessary to achieve BP control, consider adding a second agent, before proceeding to maximum doses of the first agent
- In a BP control era, for women with chronic or gestational hypertension, timed birth at 38^{+0-3} weeks may be best [WILL trial]
- Postpartum, identifying women at risk of chronic hypertension is best undertaken using early pregnancy risk factors that will remain stable targets for CV disease prevention, as efforts to prevent pre-eclampsia achieve success

Threshold for antihypertensive therapy



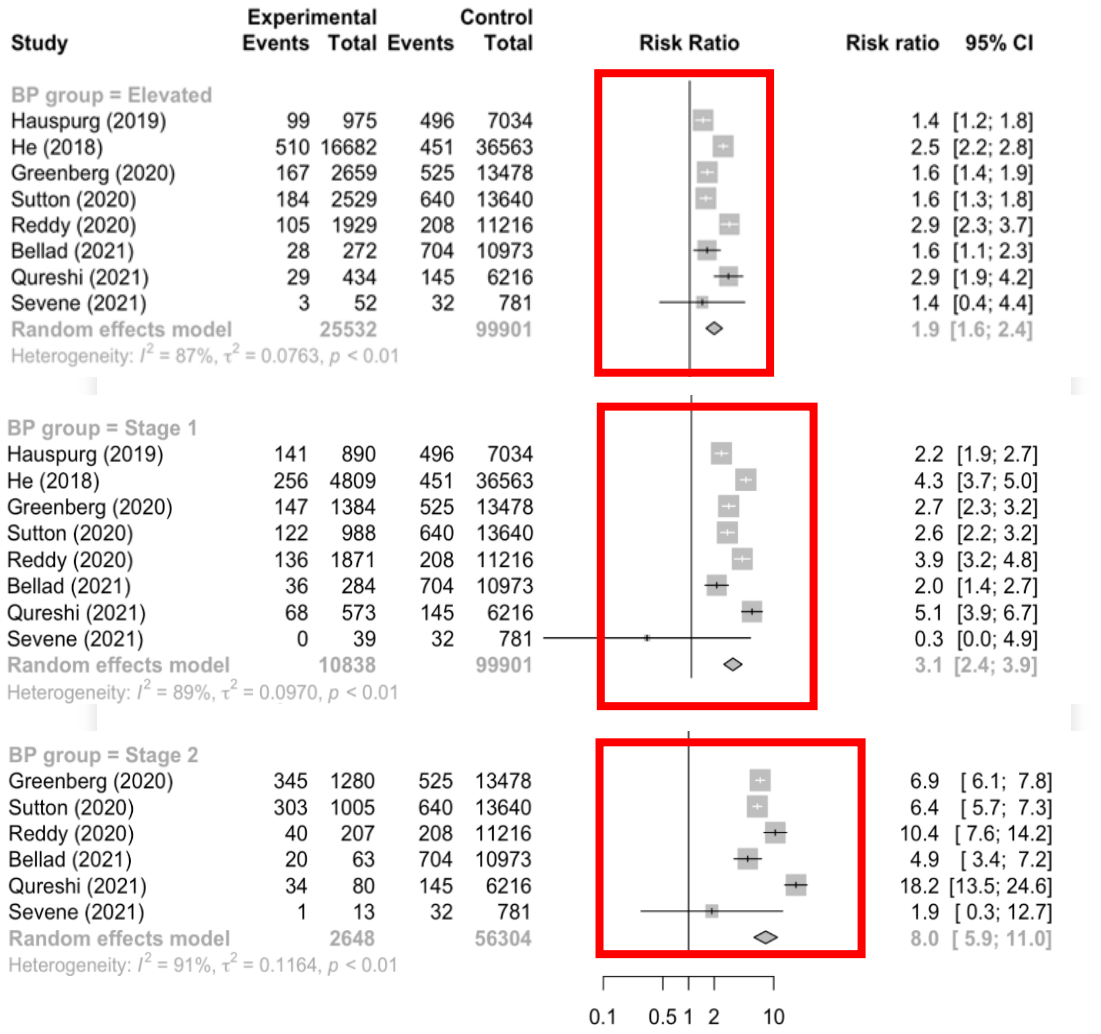
2017 ACC/AHA Criteria for Hypertension

Definition	Blood Pressure (BP)
Normal	<120/80mmHg
Elevated BP	120-129/<80mmHg
Stage 1 Hypertension	Systolic BP 130-139 or diastolic 80-89mmHg
Stage 2 Hypertension	Systolic BP ≥140 or diastolic ≥90mmHg
- Non severe	140-159/90-109mmHg
- Severe	≥160/110mmHg

Pre-eclampsia
(Strength of association)

At <20 weeks
N=23 studies,
734, 377 pregnancies)

- Higher BP was associated with more pre-eclampsia



Ref: Slade L et al. AJOG 2022 [https://doi.org/10.1016/j.ajog.2022.10.004];

Pre-eclampsia
(Diagnostic test properties of BP at <20 weeks)

- Even an 'Elevated BP' is insufficient to reassure women about development of pre-eclampsia
- Only a BP ≥140/90mmHg is sufficient to raise concern about subsequent development of pre-eclampsia
- Similar results with other adverse outcomes

Good +LR: ≥5.0

Good -LR: <0.2

Study	Ref	RR (95% CI), I^2	-LR (95% CI)	+LR (95% CI)
Diagnostic threshold: sBP 120mmHg (and dBP <80mmHg)				
Pooled	Normal (<120/80 mmHg)	**1.4 [1.1, 8.4], I^2=10%**	**0.69 [0.54, 0.82]**	**2.42 [2.07, 2.82]**
Diagnostic threshold: sBP 130mmHg or dBP 80mmHg				
Pooled	<130/80mmHg (Normal BP + Elevated BP)	**3.6 [1.4, 9.9], I^2=99%**	**0.66 [0.51, 0.78]**	**2.93 [2.32, 3.67]**
Diagnostic threshold: sBP 140mmHg or dBP 90mmHg				
Pooled	<140/90 mmHg (Normal BP + Elevated BP + Stage 1 HTN)	**5.2 (1.7,15.10), I^2=94%**	**0.80 [0.69, 0.89]**	**5.95 [4.17, 8.12]**

ACC/AHA BP values at ≥20 wks & pregnancy outcome – systematic review
12 studies, 251,172 women *[AJOG 2023; https://doi.org/10.1016/j.ajog.2023.01.013]*

Outcome		20-28 wks Study N	Women N	-LR	+LR	28-32 wks Study N	Women N	-LR	+LR	33-36 wks Study N	Women N	-LR	+LR
Diagnostic threshold: sBP 120mmHg (with dBP <80mmHg)													
Preeclampsia	**sBP≥120mmHg (dBP <80mmHg)** (<120/80 Norma	4	27,958	0.69 [0.49, 0.85]	.60 [1.94, 3.41]	4	28,645	0.58 [0.39, 0.75]	3.17 [2.41, 4.24]	4	29,192	0.46 [0.30, 0.65]	2.94 [2.27, 3.91]
Serious maternal		3	14,035	0.96 [0.91, 1.03]	.25 [0.88, 1.81]	3	13,660	0.94 [0.90, 0.98]	1.37 [1.13, 1.67]	3	13,926	0.95 [0.88, 1.02]	1.21 [0.91, 1.60]
Eclampsia		3	14,362	0.77 [0.51, 0.96]	.40 [1.30, 3.78]	3	13,932	0.80 [0.57, 0.98]	2.23 [1.13, 3.93]	3	14,180	0.90 [0.58, 1.11]	1.43 [0.55, 2.96]
Stroke			14,028	0.93 [0.66, 1.08]	.44 [0.56, 3.15]	3	13,656	0.83 [0.71, 0.94]	2.02 [1.32, 3.05]	3	13,920	0.92 [0.70, 1.08]	1.33 [0.68, 2.29]
Materna			14,025	0.95 [0.72, 1.07]	.33 [0.57, 2.72]	3	13,651	0.84 [0.54, 1.01]	2.00 [0.91, 3.55]	3	13,921	0.78 [0.52, 1.00]	1.92 [1.01, 3.10]
Cesarea			16,905	0.96 [0.95, 0.98]	.25 [1.14, 1.38]	3	13,661	0.94 [0.92, 0.96]	1.37 [1.23, 1.54]	3	13,956	0.96 [0.91, 1.02]	1.17 [0.93, 1.49]
Materna death			14,045	0.74 [0.54, 0.90]	.59 [1.56, 3.99]	3	13,680	0.79 [0.53, 0.97]	2.26 [1.23, 3.50]	3	13,948	1.00 [0.77, 1.13]	0.99 [0.44, 1.95]
Perinatal death		5	30,444	0.91 [0.81, 0.98]	.48 [1.17, 1.83]	4	28,274	0.84 [0.80, 0.88]	1.80 [1.37, 2.46]	4	28,862	0.97 [0.87, 1.12]	1.09 [0.74, 1.65]
Stillbirth		5	30,912	0.87 [0.75, 0.95]	.75 [1.32, 2.24]	4	27,608	0.81 [0.66, 0.94]	1.96 [1.21, 3.23]	4	28,751	0.89 [0.76, 1.08]	1.36 [0.84, 2.27]
Newborn death		5	29,983	0.99 [0.89, 1.03]	.08 [0.79, 1.41]	4	27,782	0.89 [0.80, 0.95]	1.51 [1.28, 1.79]	4	28,606	1.07 [0.90, 1.27]	0.76 [0.38, 1.46]
Preterm birth		5	29,675	0.96 [0.91, 0.99]	.23 [1.05, 1.43]	4	27,645	0.91 [0.82, 0.97]	1.45 [1.15, 1.84]	4	28,332	0.89 [0.78, 0.97]	1.37 [1.10, 1.70]
SGA		2	16,360	1.00 [0.95, 1.23]	.02 [0.69, 1.77]	1	14,547	1.03 [0.99, 1.07]	0.94 [0.86, 1.02]	1	15,013	0.94 [0.87, 1.01]	1.04 [1.00, 1.09]
NICU admission		2	16,451	0.91 [0.60, 1.01]	.41 [0.92, 1.69]	1	14,547	0.79 [0.68, 0.90]	1.42 [1.20, 1.65]	1	15,013	0.66 [0.50, 0.83]	1.53 [1.27, 1.77]
Diagnostic threshold: sBP 130mmHg or dBP 80mmHg													
Preeclar	**sBP≥130/80mmHg** BP <130/80 (Norma BP + Elevated		27,958	0.76 [0.59, 0.88]	.78 [2.65, 5.13]	4	28,645	0.65 [0.50, 0.78]	4.76 [3.58, 6.39]	4	29,192	0.54 [0.40, 0.68]	4.16 [3.39, 5.13]
Serious			14,035	0.96 [0.93, 1.00]	.48 [1.02, 2.16]	3	13,660	0.96 [0.94, 0.99]	1.41 [1.09, 1.84]	3	13,926	0.96 [0.90, 1.01]	1.30 [0.92, 1.85]
Eclamps			14,362	3.66 [1.67, 6.24]	0.78 [0.47, 0.96]	3	13,932	0.82 [0.55, 0.97]	3.01 [1.37, 5.52]	3	13,932	0.90 [0.48, 1.00]	6.37 [1.13,21.50]
Stroke		3	14,028	0.90 [0.69, 1.00]	.25 [1.06, 4.15]	3	13,656	0.92 [0.73, 1.00]	1.91 [0.96, 3.32]	3	13,920	0.95 [0.73, 1.06]	1.34 [0.56, 2.71]
Maternal ICU		3	14,025	0.92 [0.71, 1.02]	.01 [0.76, 4.65]	3	13,651	0.92 [0.68, 1.04]	1.88 [0.59, 5.06]	3	13,921	0.79 [0.53, 0.98]	2.45 [1.11, 4.52]
Cesarean		4	16,905	0.98 [0.96, 0.99]	.28 [1.14, 1.44]	3	13,661	0.96 [0.95, 0.98]	1.45 [1.20, 1.77]	3	13,956	0.96 [0.92, 1.00]	1.30 [1.03, 1.65]
Maternal death		3	14,045	0.94 [0.63, 1.03]	.70 [0.50, 4.29]	3	13,680	0.84 [0.66, 0.96]	2.81 [1.43, 5.10]	3	13,948	0.93 [0.68, 1.07]	1.49 [0.55, 3.42]
Perinatal death		5	30,444	0.92 [0.85, 0.96]	.93 [1.52, 2.41]	4	28,274	0.89 [0.81, 0.94]	2.11 [1.43, 3.13]	4	28,862	0.91 [0.87, 0.95]	1.52 [1.28, 1.81]
Stillbirth		5	30,912	0.89 [0.77, 0.96]	.24 [1.50, 3.16]	4	27,608	0.86 [0.71, 0.96]	.42 [1.34, 4.24]	4	28,591	0.86 [0.79, 0.93]	1.86 [1.33, 2.64]
Newborn death		5	29,983	0.96 [0.93, 0.99]	.40 [1.13, 1.73]	4	27,782	0.94 [0.90, 0.97]	1.63 [1.23, 2.16]	4	28,606	0.99 [0.84, 1.07]	1.09 [0.58, 1.89]
Preterm birth		5	29,675	0.96 [0.94, 0.98]	.43 [1.23, 1.63]	4	27,645	0.93 [0.87, 0.98]	1.69 [1.24, 2.30]	4	28,332	0.91 [0.79, 0.98]	1.60 [1.12, 2.19]
SGA		2	16,360	0.98 [0.93, 1.07]	.16 [0.67, 2.11]	1	14,547	0.98 [0.96, 1.01]	1.08 [0.95, 1.22]	1	15,013	1.00 [0.97, 1.03]	1.01 [0.91, 1.12]
NICU admission		2	16,451	0.93 [0.74, 1.00]	.64 [0.99, 2.36]	1	14,547	0.79 [0.71, 0.87]	2.07 [1.65, 2.53]	1	15,013	0.74 [0.61, 0.87]	1.91 [1.48, 2.37]
Diagnostic threshold: sBP 140mmHg or dBP 90mmHg													
Preeclampsia	**sBP≥140/90mmHg** <14 /90mmHg (Normal BP + Ele ated BP + Stage	4	27,958	0.89 [0.79, 0.94]	4.70 7.17,28.80]	4	28,645	0.83 [0.69, 0.92]	18.20 8.03,39.20]	4	29,192	0.74 [0.65, 0.82]	15.30 [8.10, 28.20]
Serious			14,035	0.99 [0.97, 1.00]	.96 [1.02, 3.77]	3	13,660	1.00 [0.98, 1.00]	1.26 [0.85, 1.88]	3	13,926	0.99 [0.94, 1.01]	1.51 [0.76, 2.96]
Eclamps			14,362	0.90 [0.74, 0.98]	7.82 [2.73, 19.8]	3	13,932	0.90 [0.48, 1.00]	6.37 [1.13, 21.50]	3	13,932	0.86 [0.65, 0.97]	5.78 [2.20, 12.90
Stroke		3	14,028	0.94 [0.86, 0.98]	.40 [2.57, 10.9]	3	13,656	0.92 [0.84, 0.97]	.29 [2.27, 12.00]	3	13,920	0.88 [0.70, 0.97]	5.00 [1.99, 10.90
Maternal ICU		3	14,025	0.96 [0.78, 1.00]	3.88 [0.76, 16.8]	3	13,651	0.91 [0.69, 0.99]	.97 [1.70, 17.90}	3	13,921	0.87 [0.63, 0.98]	5.45 [1.77, 13.80
Cesarean		4	16,905	1.71 [1.14, 2.56]	0.99 [0.99, 1.00]	3	13,661	1.00 [0.96, 1.00]	1.29 [0.70, 2.34]	3	13,956	0.99 [0.98, 0.99]	1.49 [1.19, 1.86]
Maternal death		3	14,045	0.93 [0.77, 0.99]	.21 [2.10, 16.3]	3	13,680	0.92 [0.76, 0.98]	.52 [1.92, 14.50]	3	13,948	0.86 [0.67, 0.96]	5.77 [2.32, 12.40
[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Stillbirth		5	30,912	0.94 [0.92, 0.96]	6.36 [4.72, 8.54]	4	27,608	0.94 [0.87, 0.98]	5.16 [1.96,13.10]	4	28,591	0.90 [0.85, 0.93]	4.69 [3.46, 6.28]
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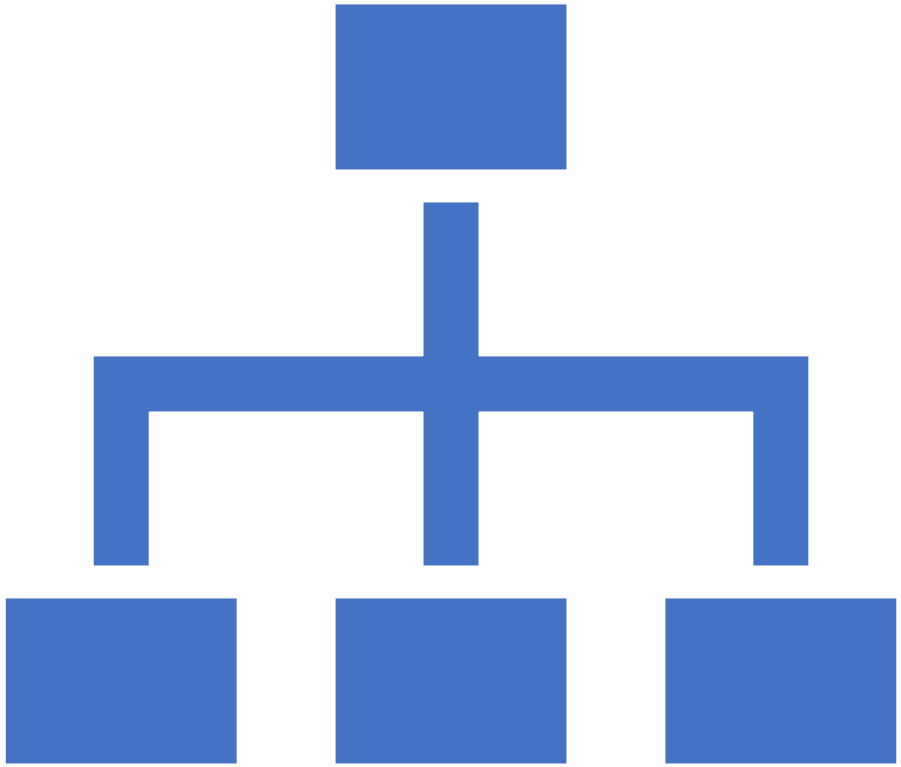
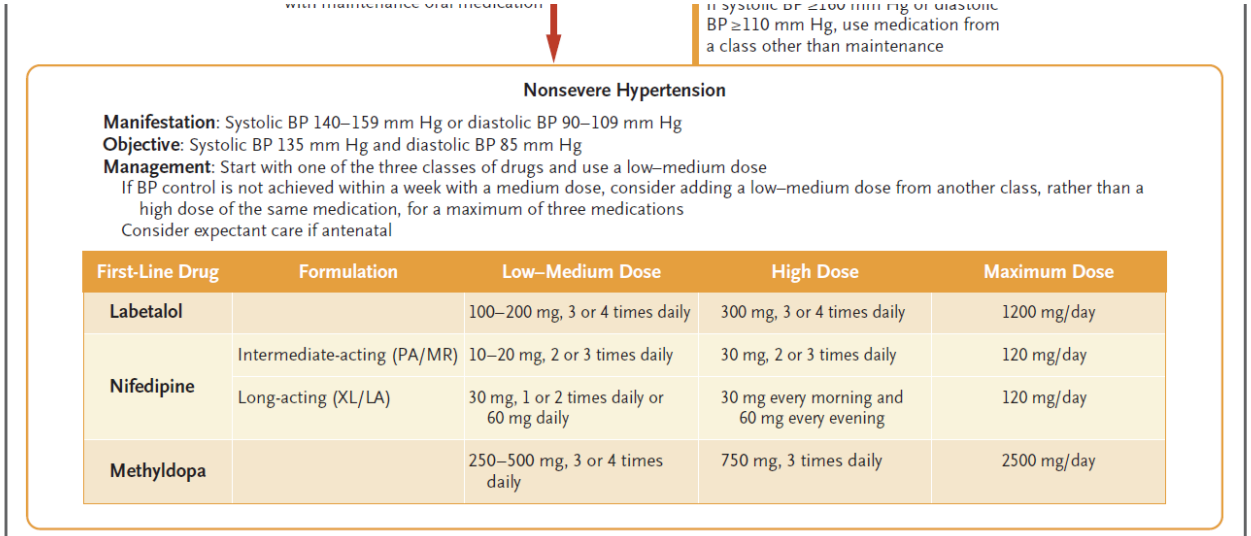
SGA		2	16,360	1.00 [0.99, 1.01]	1.12 [0.52, 2.44]	1	14,547	0.99 [0.98, 1.00]	1.64 [1.18, 2.28]	1	15,013	0.99 [0.97, 1.00]	1.46 [1.12, 1.89]
NICU admission		2	16,451	0.99 [0.91, 1.00]	2.22 [0.59, 7.80]	1	14,547	0.85 [0.78, 0.89]	9.57 [6.70, 13.40]	1	15,013	0.93 [0.84, 0.97]	3.27 [1.77, 5.77]

Antihypertensive therapy

Severe hypertension



First-Line Drug	Route of Administration and Dosage Units	0 Min	30 Min	60 Min	90 Min	120 Min	150 Min
Labetalol	Oral — mg	200	—	200	—	200	—
	Intermittent IV — mg	10–20	20–40	40–80	40–80	40–80	40–80
	IV infusion — mg/min	0.5–2.0	→	→	→	→	→
Nifedipine	Oral capsule — mg	5–10	10	—	10	—	10
	Oral tablet (PA/MR) — mg	10	—	10	—	10	—
Hydralazine	Intermittent IV — mg	5	5–10	5–10	5–10	—	—
Methyldopa	Oral (if other medications unavailable or for in utero transfer without monitoring) — mg	1000	—	—	—	—	—



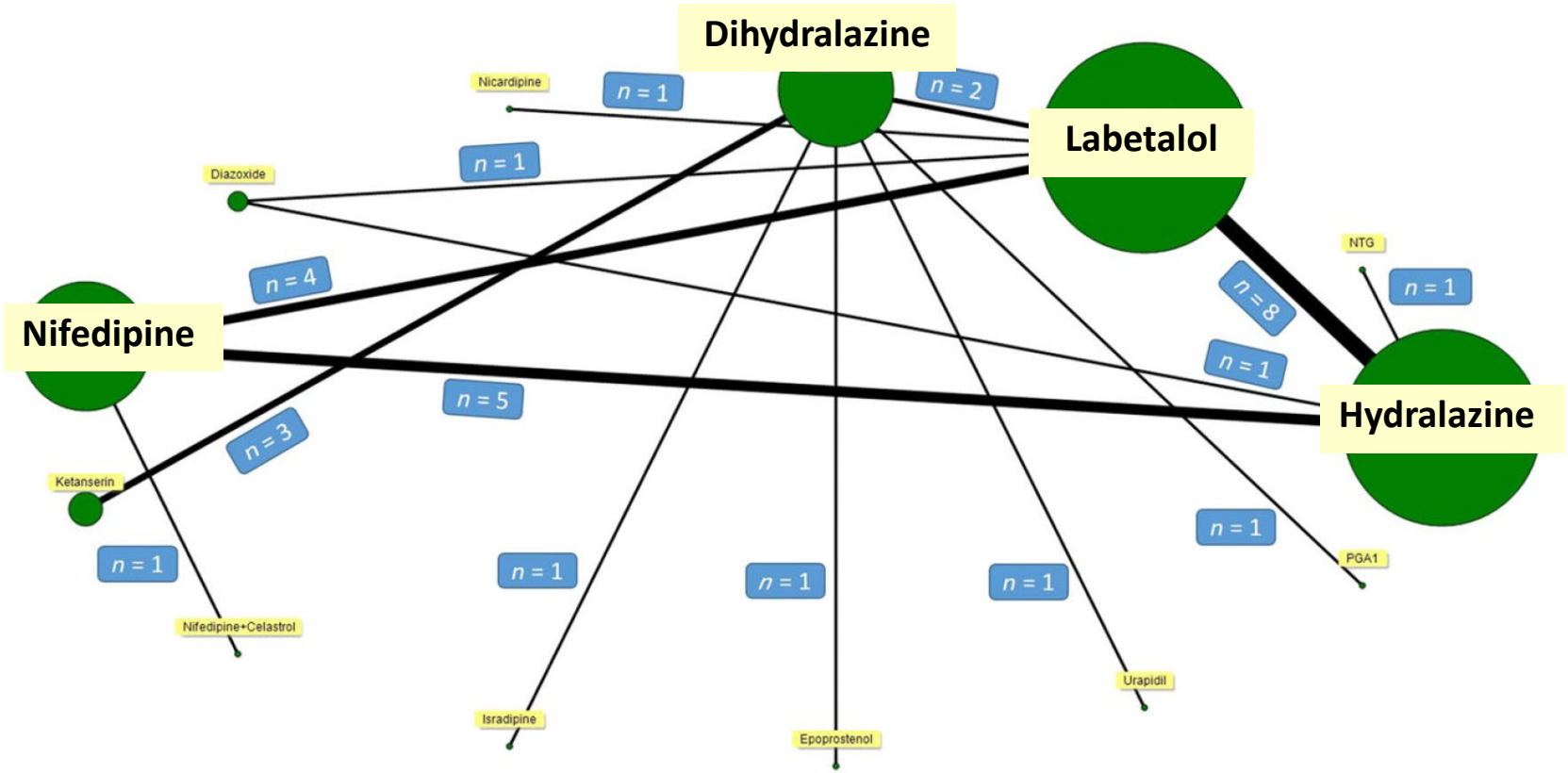
First-Line Drug	Formulation	Low–Medium Dose	High Dose	Maximum Dose
Labetalol		100–200 mg, 3 or 4 times daily	300 mg, 3 or 4 times daily	1200 mg/day
Nifedipine	Intermediate-acting (PA/MR)	10–20 mg, 2 or 3 times daily	30 mg, 2 or 3 times daily	120 mg/day
	Long-acting (XL/LA)	30 mg, 1 or 2 times daily or 60 mg daily	30 mg every morning and 60 mg every evening	120 mg/day
Methyldopa		250–500 mg, 3 or 4 times daily	750 mg, 3 times daily	2500 mg/day

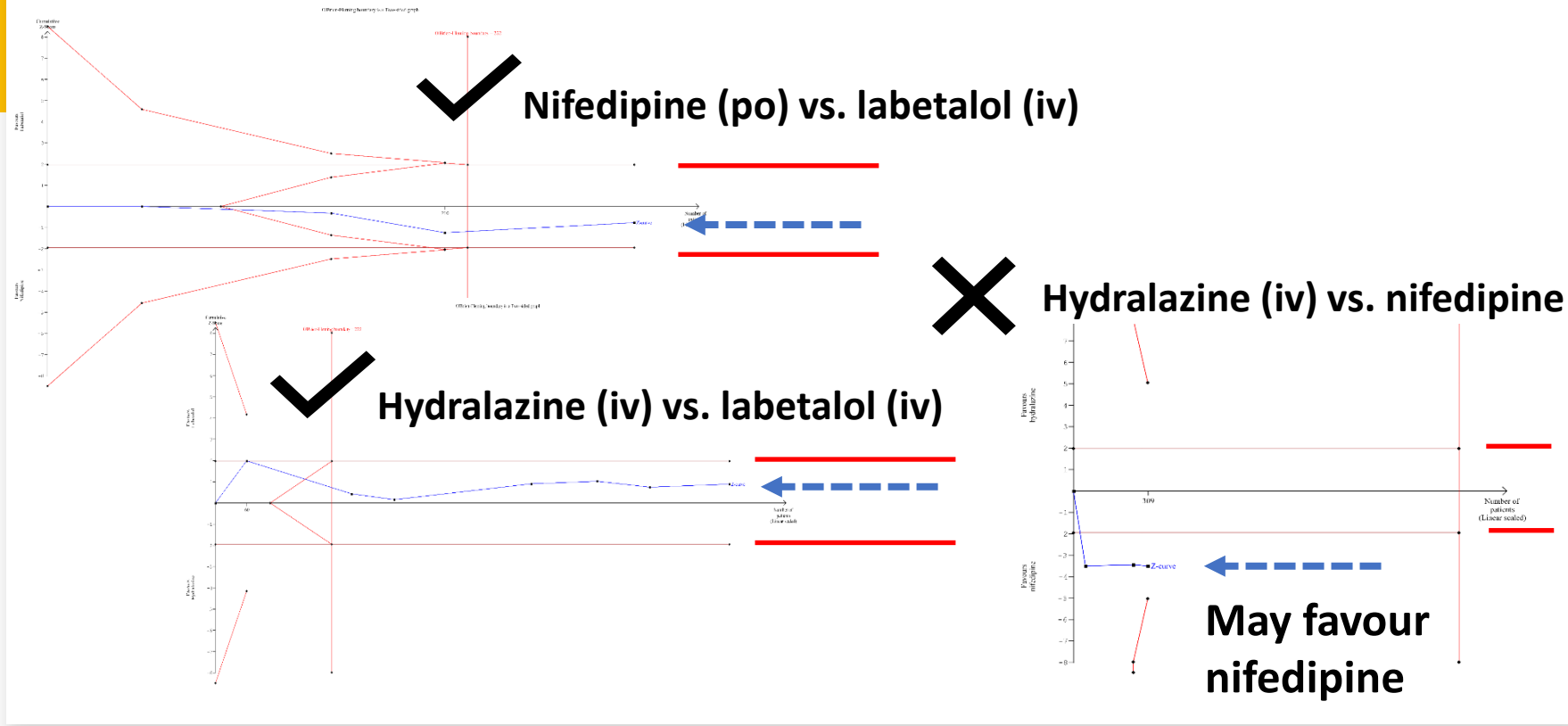
Figure 3. **Management of Blood Pressure.**
The information presented is modified from Magee et al.[24] Severe hypertension (systolic BP ≥160 mm Hg or diastolic BP ≥110 mm Hg) requires urgent treatment, as shown in the red box. Oral or parenteral treatment is administered to achieve a target BP of less than 160/110 mm Hg within a few hours. In the hours that follow, a BP of 135/85 mm Hg is the target, with the approach shown in the orange box. ICU denotes intensive care unit, IV intravenous, LA long-acting, MR modified release, PA prolonged action, and XL extended length of action.

von Dadelszen. *NEJM* 2022; 386:1817

Antihypertensive therapy for severe hypertension

Network meta-analysis NMA [Sridharan *et al*. *BJCP* 2018]

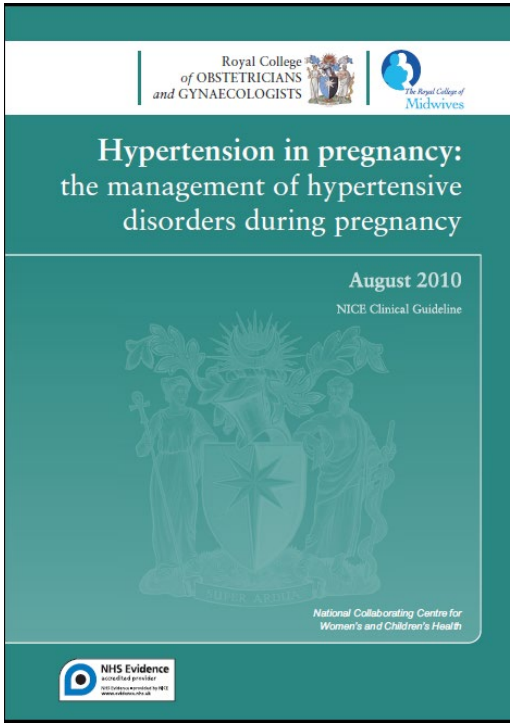


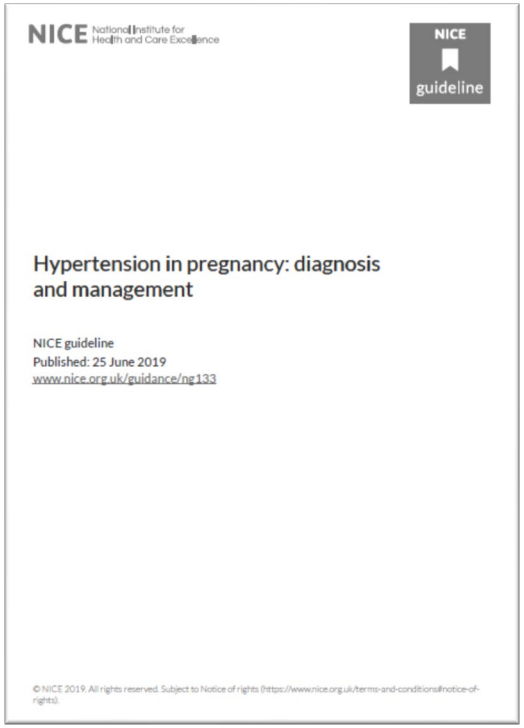


Severe hypertension

Network meta-analysis NMA [Sridharan et al. BJCP 2018]

- **Trial sequential analysis to see whether enough confidence had accumulated to be sure of finding a relative risk reduction of 10% if such a difference existed (when there was a minimum of 5 trials)**





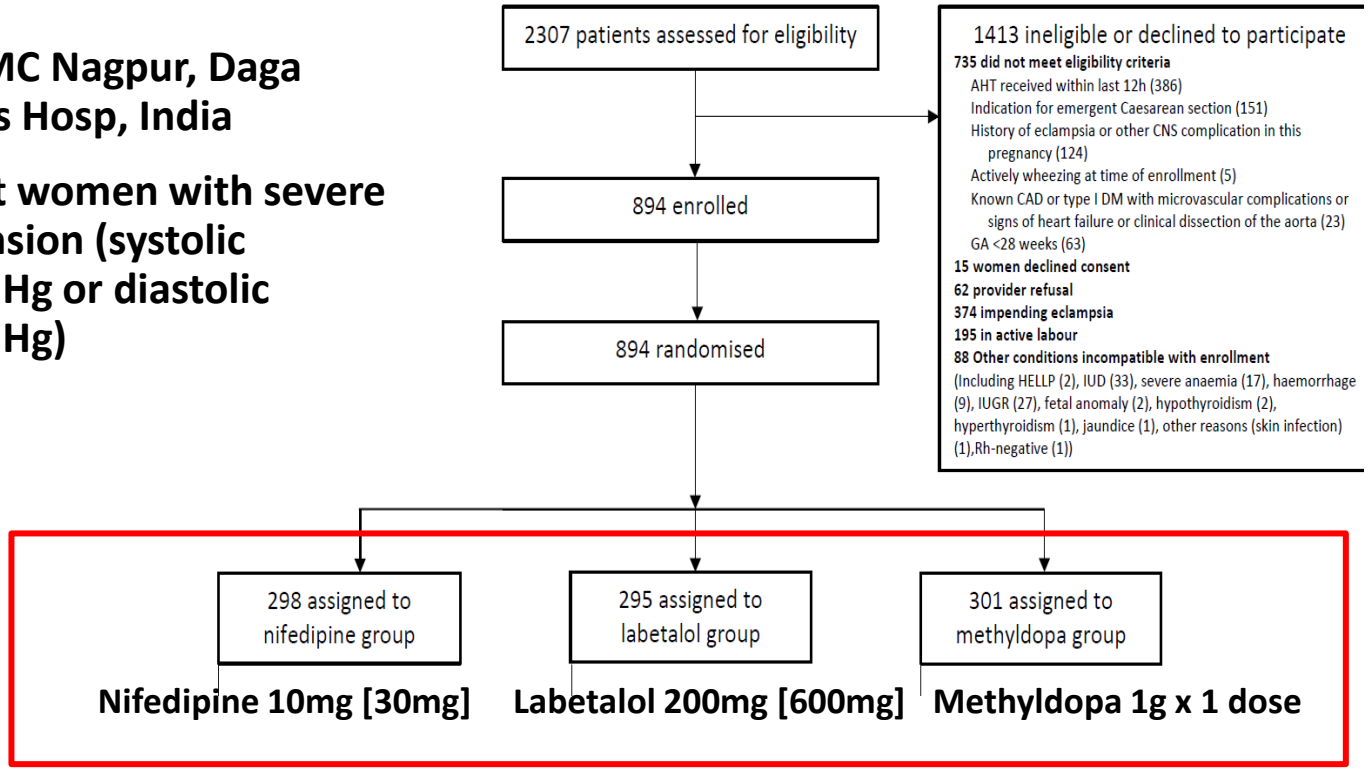
Oral labetalol

NICE CG107 2010
Updated NG133 2019

- **Treat women with severe hypertension who are in a critical care setting during pregnancy or after birth immediately with one of the following:**
  - **labetalol (oral or intravenous)**
  - **nifedipine (oral)**
  - **hydralazine (intravenous)**

Gynuity Health Projects Oral Antihypertensive trial
(Bracken *et al. Lancet* 2019)

- **Sites: GMC Nagpur, Daga Women's Hosp, India**
- **Pregnant women with severe hypertension (systolic ≥160mmHg or diastolic ≥110mmHg)**



- **Results:**
  - **1° - In-target BP (120-150/70-100) without fetal compromise at 6 hours**
    - **Nifedipine 83.6%**
    - **Labetalol 77.3%**
    - **Methyldopa 76.4% (NvM p=0.03)**
  - **2° - 1° outcome without additional medication**
    - **Nifedipine 82.9% (NvM p<0.01)**
    - **Labetalol 10.3% (NvL p<0.001)**
    - **Methyldopa 9.9% (NvM p<0.01)**
  - **Other: indication for NICU admission = LBW/VLBW**
    - **Nifedipine 12.4%**
    - **Labetalol 5.9% (NvL p<0.01)**
    - **Methyldopa 6.8% (NvM p=0.03)**

Success in ≥75%

Success with single drug >60%

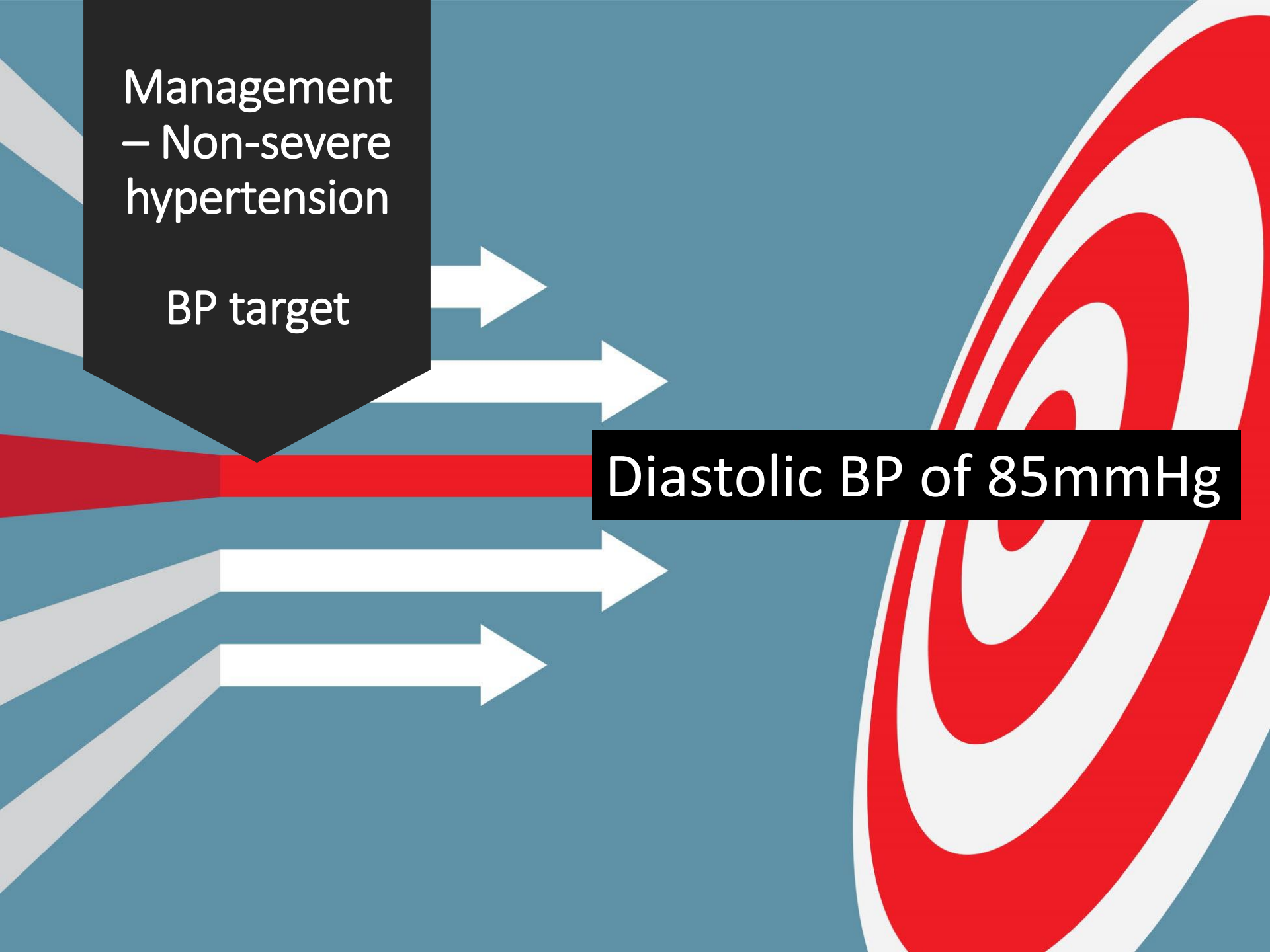
Gynuity Health Projects Oral Antihypertensive trial (Bracken *et al.* *Lancet* 2019)

Gynuity HEALTH PROJECTS

PRE-EMPT
Pre-eclampsia and eclampsia monitoring, prevention & treatment

Management – Non-severe hypertension

BP target



Antihypertensive therapy for non-severe hypertension

[*Lancet* 2000;355:87-92]

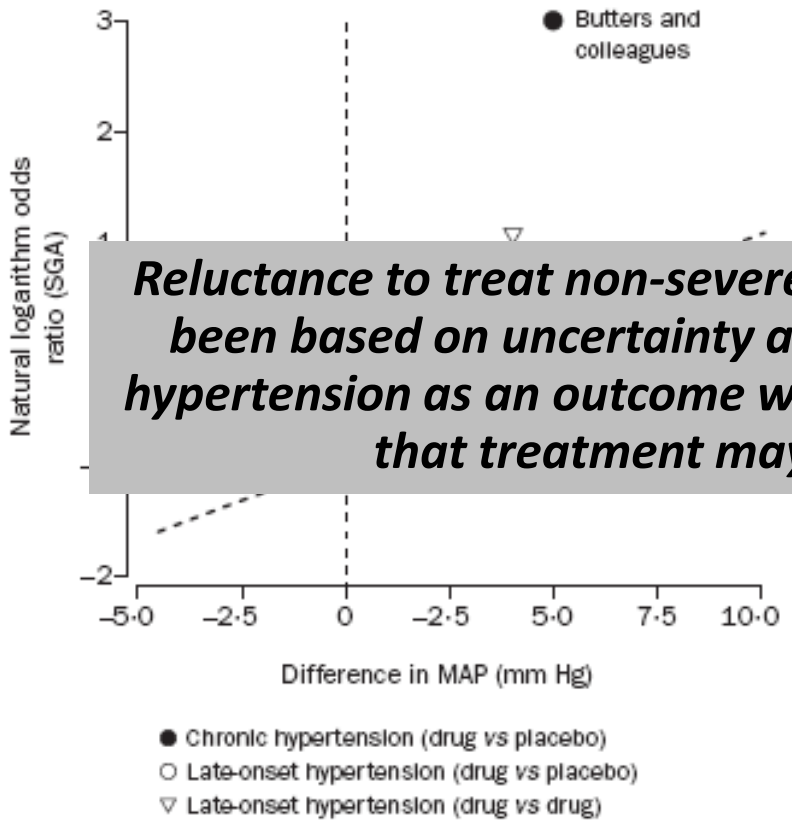


Figure 1: **Relation between fall in MAP and proportion of SGA infants**

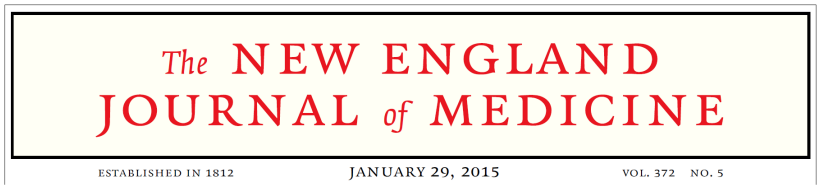
Spearman's ρ=0·69 (p=0·007) without Butters and colleagues' trial,[4] ρ=0·64 (p=0·01) with that trial.

- **RCTs showed long ago that antihypertensive therapy in pregnancy reduces the incidence of severe**

Reluctance to treat non-severe hypertension in pregnancy has been based on uncertainty about the importance of severe hypertension as an outcome worthy of avoidance, and concern that treatment may impair fetal growth

lysis
t or
another antihypertensive) showed that a greater antihypertensive-induced fall in MAP was associated with a higher incidence of SGA infants

CHIPS Trial (Control of Hypertension in Pregnancy Study) 2009-2012 (NEJM 2015)



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 29, 2015 VOL. 372 NO. 5

Less-Tight versus Tight Control of Hypertension in Pregnancy

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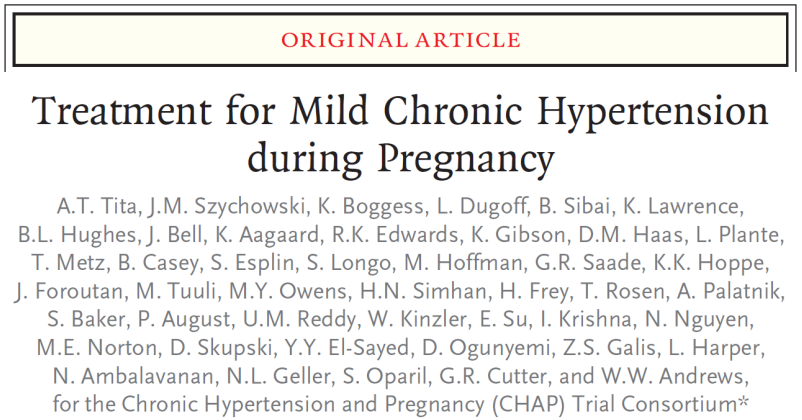
CHAP Trial (Chronic Hypertension And Pregnancy) 2015-2021 (NEJM 2022; 2 Apr)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

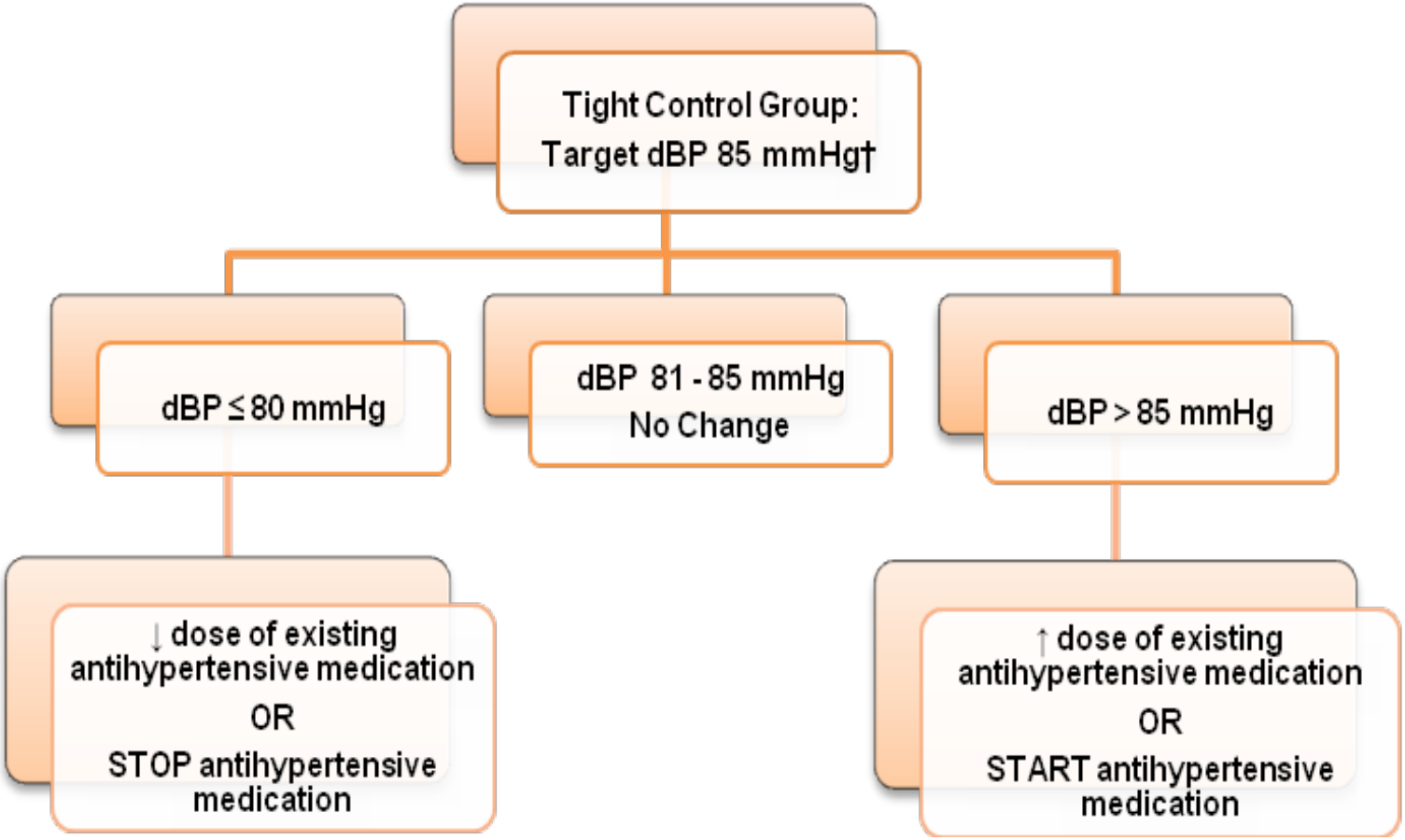
Treatment for Mild Chronic Hypertension during Pregnancy

A.T. Tita, J.M. Szychowski, K. Boggess, L. Dugoff, B. Sibai, K. Lawrence, B.L. Hughes, J. Bell, K. Aagaard, R.K. Edwards, K. Gibson, D.M. Haas, L. Plante, T. Metz, B. Casey, S. Esplin, S. Longo, M. Hoffman, G.R. Saade, K.K. Hoppe, J. Foroutan, M. Tuuli, M.Y. Owens, H.N. Simhan, H. Frey, T. Rosen, A. Palatnik, S. Baker, P. August, U.M. Reddy, W. Kinzler, E. Su, I. Krishna, N. Nguyen, M.E. Norton, D. Skupski, Y.Y. El-Sayed, D. Ogunyemi, Z.S. Galis, L. Harper, N. Ambalavanan, N.L. Geller, S. Oparil, G.R. Cutter, and W.W. Andrews, for the Chronic Hypertension and Pregnancy (CHAP) Trial Consortium*

- **CHIPS: 'Less tight' vs. 'tight' BP control of chronic or gestational hypertension**
- **CHAP: Control of chronic hypertension vs. usual care**
- **CHIPS: No impact on primary outcome (of pregnancy loss or high-level neonatal care for >48 hr) or secondary outcome (of serious maternal complications), but significant decrease in severe hypertension, platelets <100,000, and elevated liver enzymes with symptoms**
- **CHAP: Reduction in primary composite (pre-eclampsia with 'severe features', medically indicated delivery <35+0 wk, abruption, or perinatal death)**
- **Neither trial demonstrated an increase in BW <10th percentile**

‘Tight’ control (dBP goal of 85mmHg)

BP achieved was 133/85mmHg



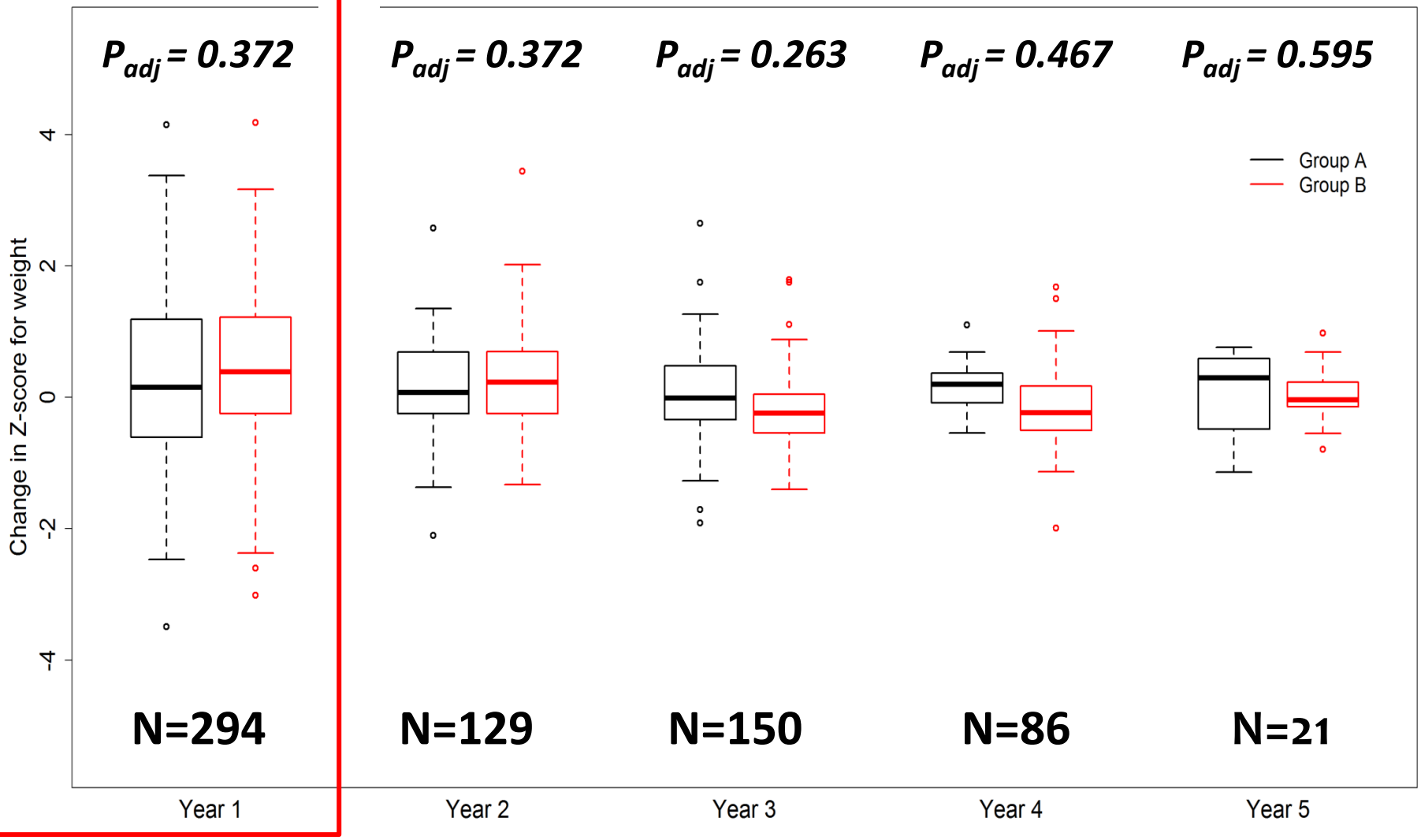
Increase dose or START new medication if sBP ≥160mmHg

CHIPS & CHAP have complementary strengths

	CHIPS (NEJM 2015)	CHAP (NEJM 2022)
Recruitment period	2009-12	2015-21
N women	987	2408
Trial characteristics		
N countries	16 (includes Qatar)	1 (United States)
N sites	95 (includes Qatar)	“>70”
RCT design	Individual, 1:1 randomisation	Individual, 1:1 randomisation
Participants		
Type hypertension	Chronic hypertension* (75%) Gestational hypertension (25%)	Chronic hypertension*
Ethnicity	Caucasian (64.3 vs. 60.0%) Black (12.4 vs. 12.5%) Asian (9.4 vs. 12.5%) Hispanic (12.9 vs. 11.7%)	White non-Hispanic (28.7 vs. 27.2%) Black (47.5 vs. 47.5%) Asian (not specifically reported) Hispanic (19.7 vs. 20.8%)
BMI <30	50.3 vs. 51.3%	21.6 vs. 24.4%
Diabetes	Excluded	15.8 vs. 15.8%
Intervention	‘Tight’ BP control (target dBP 85mmHg)	<140/90mmHg
Control	‘Less tight’ BP control (target dBP 100mmHg)	Standard BP control (antihypertensives withheld or stopped unless BP ≥160/105mmHg, then target <140/90mmHg)
Antihypertensives	92.6% vs. 73.4% Labetalol (67.3 vs. 66.9% antenatally) Nifedipine (30.1 vs. 31.8%) Methyldopa (40.3 vs. 42.5% antenatally)	88.9% vs. 24.4% Labetalol (63.2 vs. 61.6%) Nifedipine (33.4 vs. 30.6%) Methyldopa (1.4 vs. 0.5%)

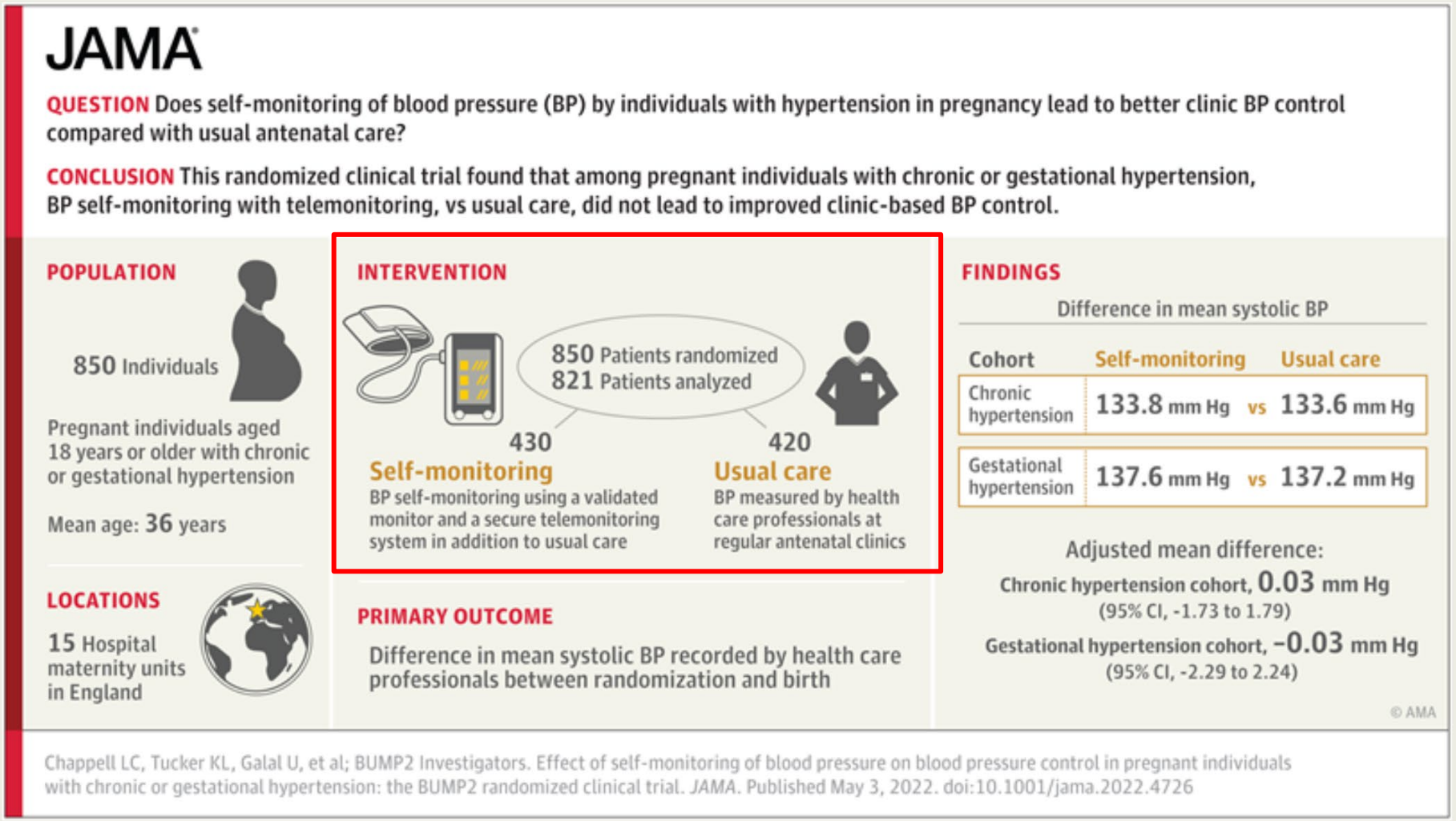
CHIPS-Child: Change in z-score for weight by year compared *with year before*

Mixed effects regression: No compelling evidence for developmental programming of growth



Is BP control improved by home BP monitoring for women with chronic or gestational hypertension

(BUMP2 trial: *JAMA* 2022;327(17):1666-78; NCT03334149)



Chappell LC, Tucker KL, Galal U, et al; BUMP2 Investigators. Effect of self-monitoring of blood pressure on blood pressure control in pregnant individuals with chronic or gestational hypertension: the BUMP2 randomized clinical trial. *JAMA*. Published May 3, 2022. doi:10.1001/jama.2022.4726

Among women with chronic hypertension (N=454), fewer in intervention group experienced spontaneous onset labour: 5% vs. 10%; aOR 0.52 [0.29-0.93]

How do clinic and home BP readings compare in pregnancy? (*Hypertension* 2018;72:686-694)

All women (Fig 2)

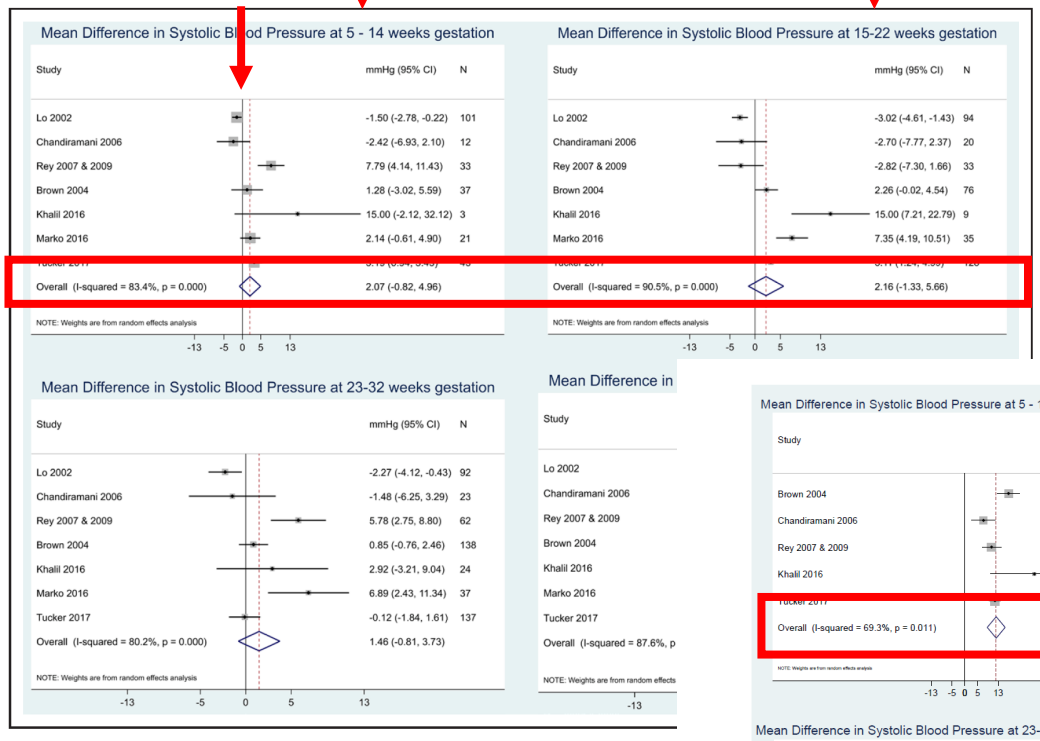
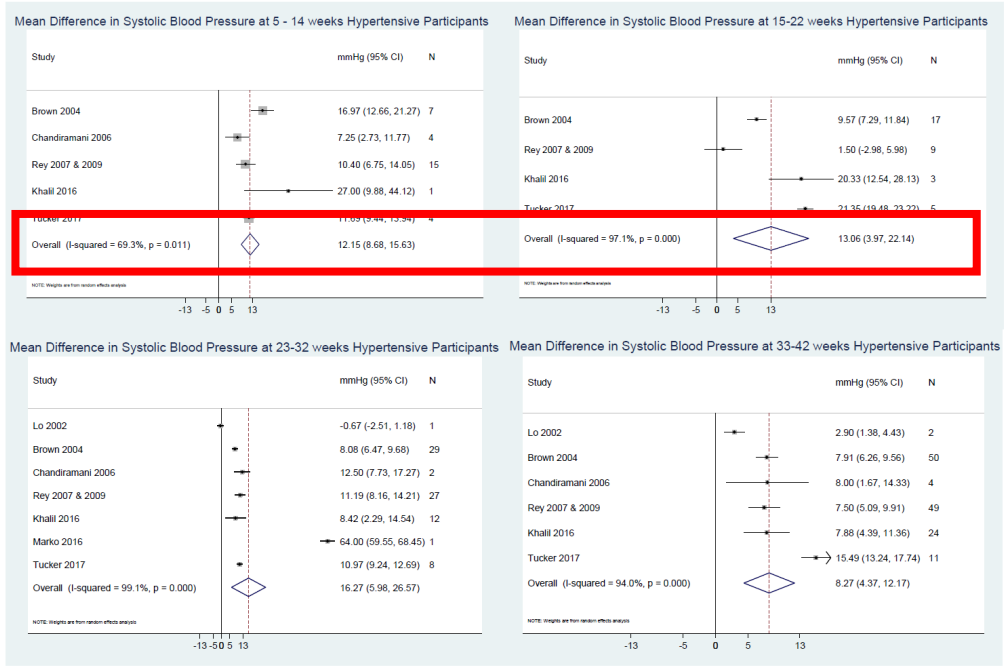


Figure 2. Comparison of clinic and self-monitored systolic blood pressure (BP). Forest plots were cons
home) by the type of monitoring and study group. Data were analyzed as continuous variables and pre
indicates confidence interval.

Hypertensive women (Fig S7)



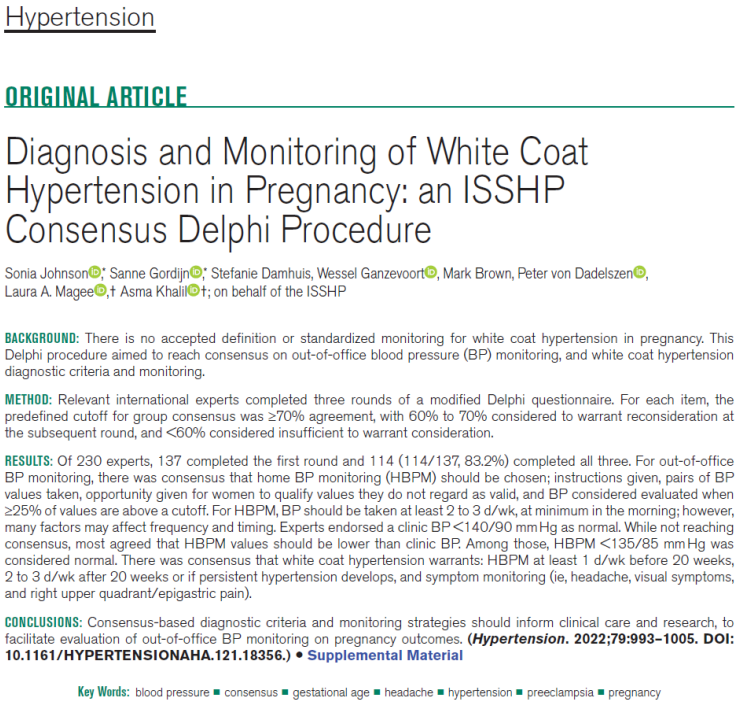
Home BP monitoring

Delphi consensus (*Hypertension* 2022;79:993-1005)

- Eligibility for participation was based on meeting at least one of three inclusion criteria:

1. Expertise in WCH or HBPM, based on publications (including guidelines), through PubMed and Research Gate
2. Membership in ISSHP or affiliated scientific organisations, such as the Macdonald Obstetric Medicine Society, International Society of Obstetric Medicine, Society of Obstetric Medicine Australian and New Zealand and World Gestosis, among others
3. We asked invitees for suggestions of others with relevant expertise in the area

- Potentially eligible participants were sent an invitational email
- Of 230 experts, 137 completed the first round and 114 (114/137, 83.2%) completed all three



Hypertension

ORIGINAL ARTICLE

Diagnosis and Monitoring of White Coat Hypertension in Pregnancy: an ISSHP Consensus Delphi Procedure

Sonia Johnson, Sanne Gordijn, Stefanie Damhuis, Wessel Ganzevoort, Mark Brown, Peter von Dadelszen, Laura A. Magee, Asma Khalil; on behalf of the ISSHP

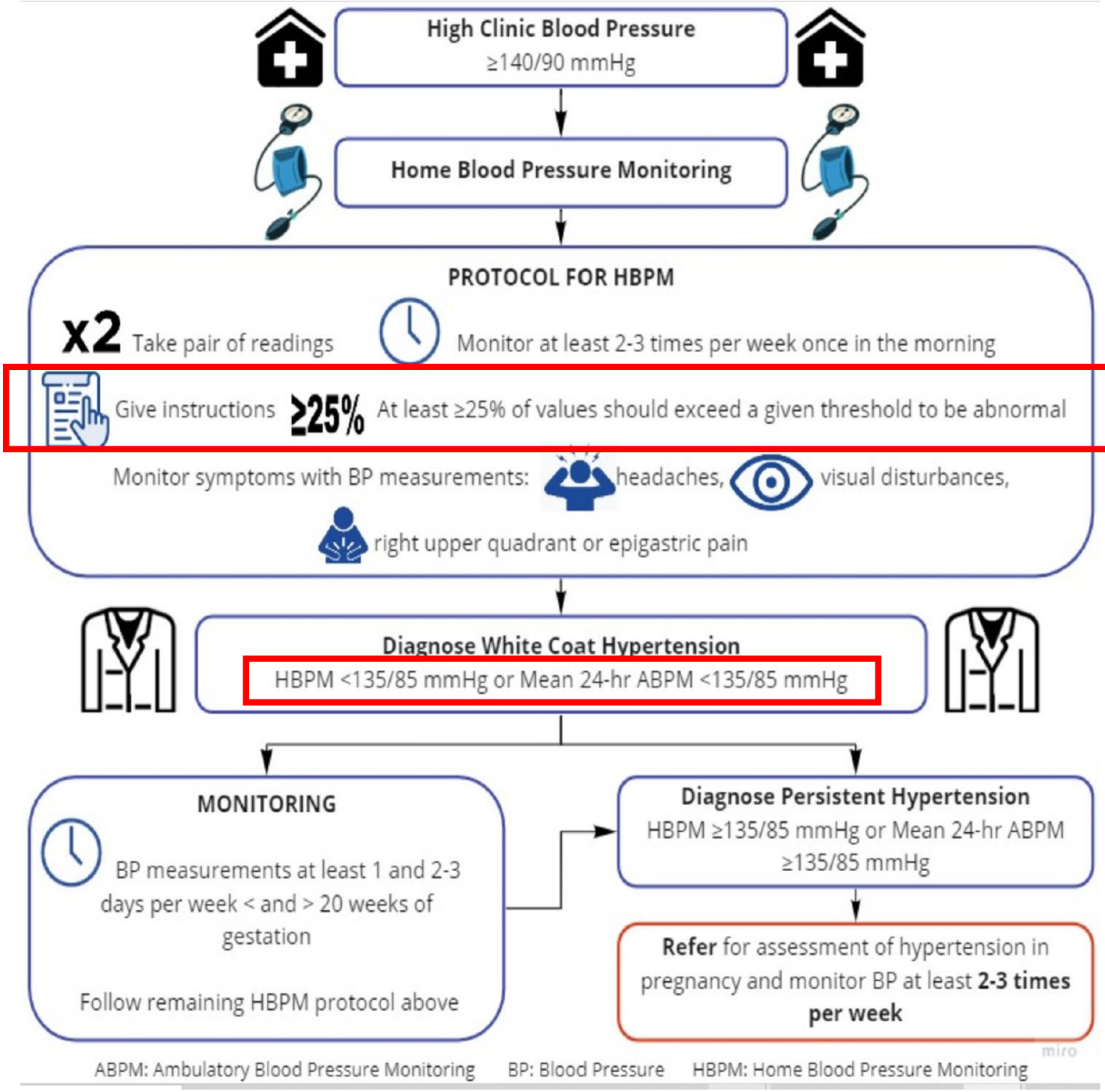
BACKGROUND: There is no accepted definition or standardized monitoring for white coat hypertension in pregnancy. This Delphi procedure aimed to reach consensus on out-of-office blood pressure (BP) monitoring, and white coat hypertension diagnostic criteria and monitoring.

METHOD: Relevant international experts completed three rounds of a modified Delphi questionnaire. For each item, the predefined cutoff for group consensus was ≥70% agreement, with 60% to 70% considered to warrant reconsideration at the subsequent round, and <60% considered insufficient to warrant consideration.

RESULTS: Of 230 experts, 137 completed the first round and 114 (114/137, 83.2%) completed all three. For out-of-office BP monitoring, there was consensus that home BP monitoring (HBPM) should be chosen; instructions given, pairs of BP values taken, opportunity given for women to qualify values they do not regard as valid, and BP considered evaluated when ≥25% of values are above a cutoff. For HBPM, BP should be taken at least 2 to 3 d/wk, at minimum in the morning; however, many factors may affect frequency and timing. Experts endorsed a clinic BP <140/90 mm Hg as normal. While not reaching consensus, most agreed that HBPM values should be lower than clinic BP. Among those, HBPM <135/85 mm Hg was considered normal. There was consensus that white coat hypertension warrants: HBPM at least 1 d/wk before 20 weeks, 2 to 3 d/wk after 20 weeks or if persistent hypertension develops, and symptom monitoring (ie, headache, visual symptoms, and right upper quadrant/epigastric pain).

CONCLUSIONS: Consensus-based diagnostic criteria and monitoring strategies should inform clinical care and research, to facilitate evaluation of out-of-office BP monitoring on pregnancy outcomes. (***Hypertension***. **2022;79:993–1005. DOI: 10.1161/HYPERTENSIONAHA.121.18356.)** • **Supplemental Material**

Key Words: blood pressure ■ consensus ■ gestational age ■ headache ■ hypertension ■ preeclampsia ■ pregnancy


High Clinic Blood Pressure
≥140/90 mmHg
Home Blood Pressure Monitoring
PROTOCOL FOR HBPM
x2 Take pair of readings
Monitor at least 2-3 times per week once in the morning
Give instructions
≥25%
At least ≥25% of values should exceed a given threshold to be abnormal
Monitor symptoms with BP measurements:
headaches,
visual disturbances,
right upper quadrant or epigastric pain
Diagnose White Coat Hypertension
HBPM <135/85 mmHg or Mean 24-hr ABPM <135/85 mmHg
MONITORING
BP measurements at least 1 and 2-3 days per week < and > 20 weeks of gestation
Follow remaining HBPM protocol above
Diagnose Persistent Hypertension
HBPM ≥135/85 mmHg or Mean 24-hr ABPM ≥135/85 mmHg
Refer for assessment of hypertension in pregnancy and monitor BP at least 2-3 times per week
ABPM: Ambulatory Blood Pressure Monitoring
BP: Blood Pressure
HBPM: Home Blood Pressure Monitoring

Management – non-severe hypertension

How do antihypertensives compare?

~~Which antihypertensive is best?~~

How do antihypertensive therapies compare?

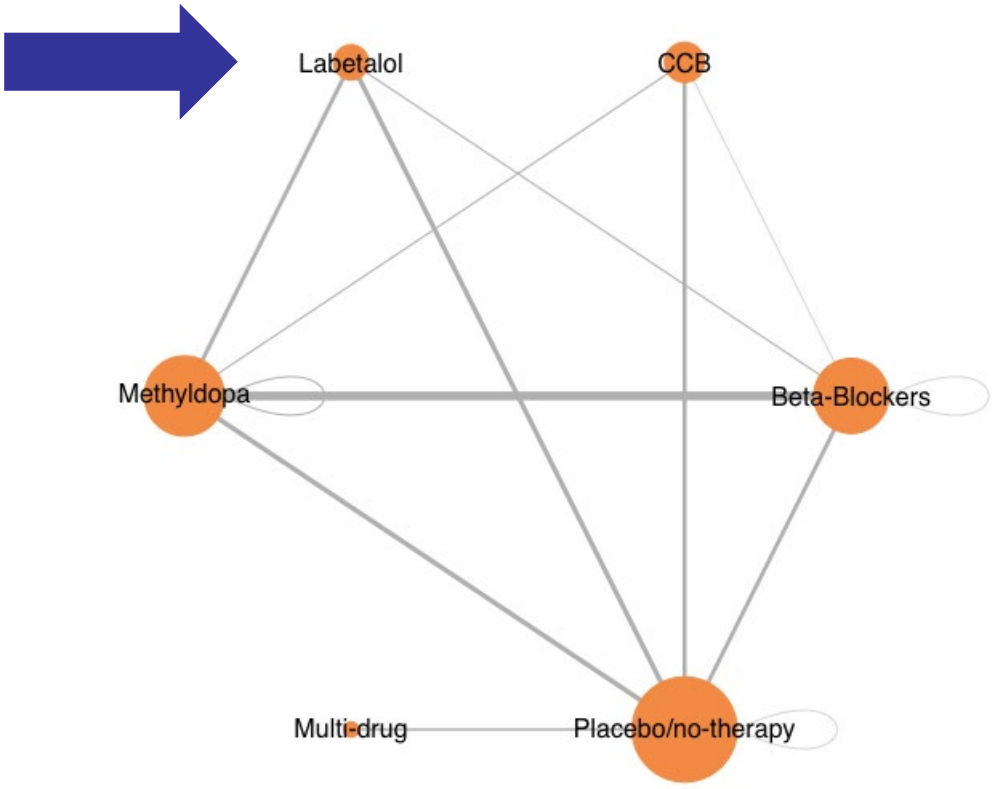
Network meta-analysis

(N=32 trials, 3811 women)

***Hypertension* 2022 Mar;79(3):614-628**

72 trials were included;

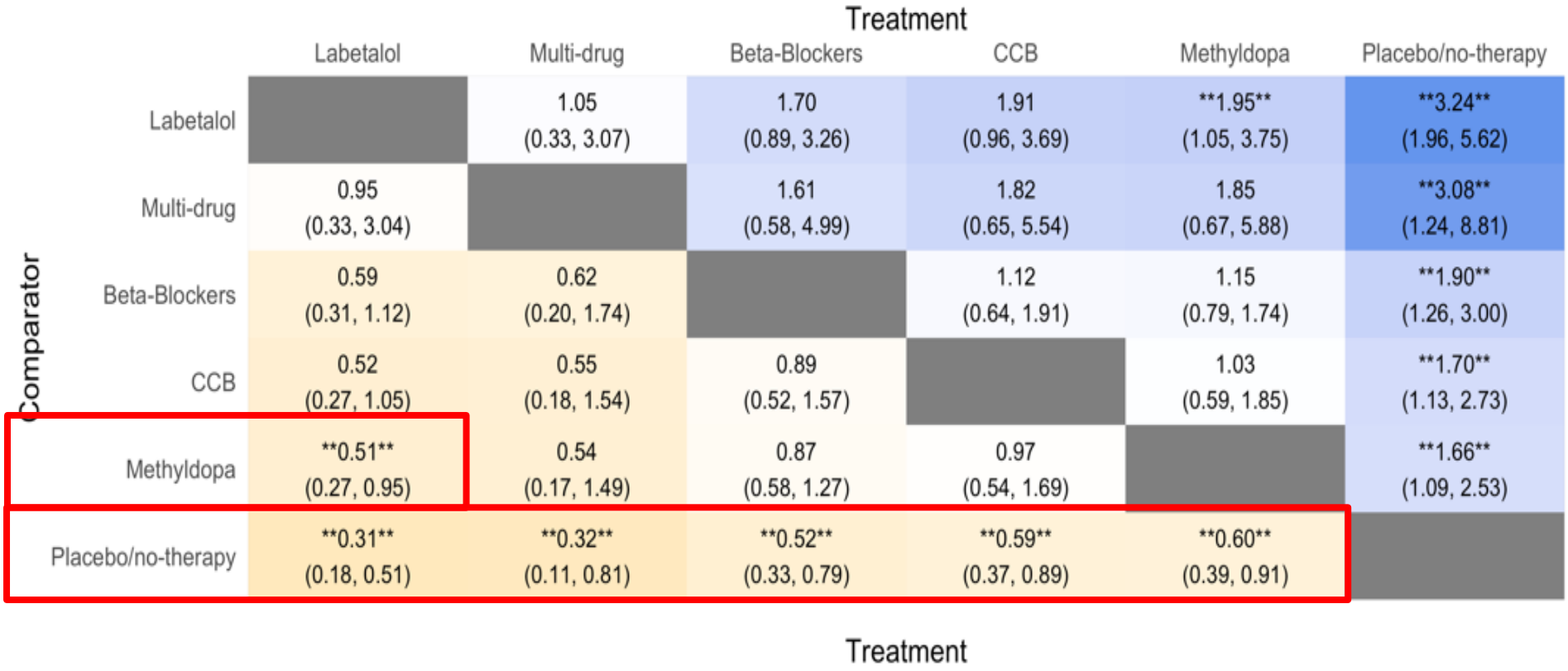
61 (6923 women) were informative



Network meta-analysis (N=32 trials, 3811 women)

Severe hypertension (median 13%, IQR 7-22%)

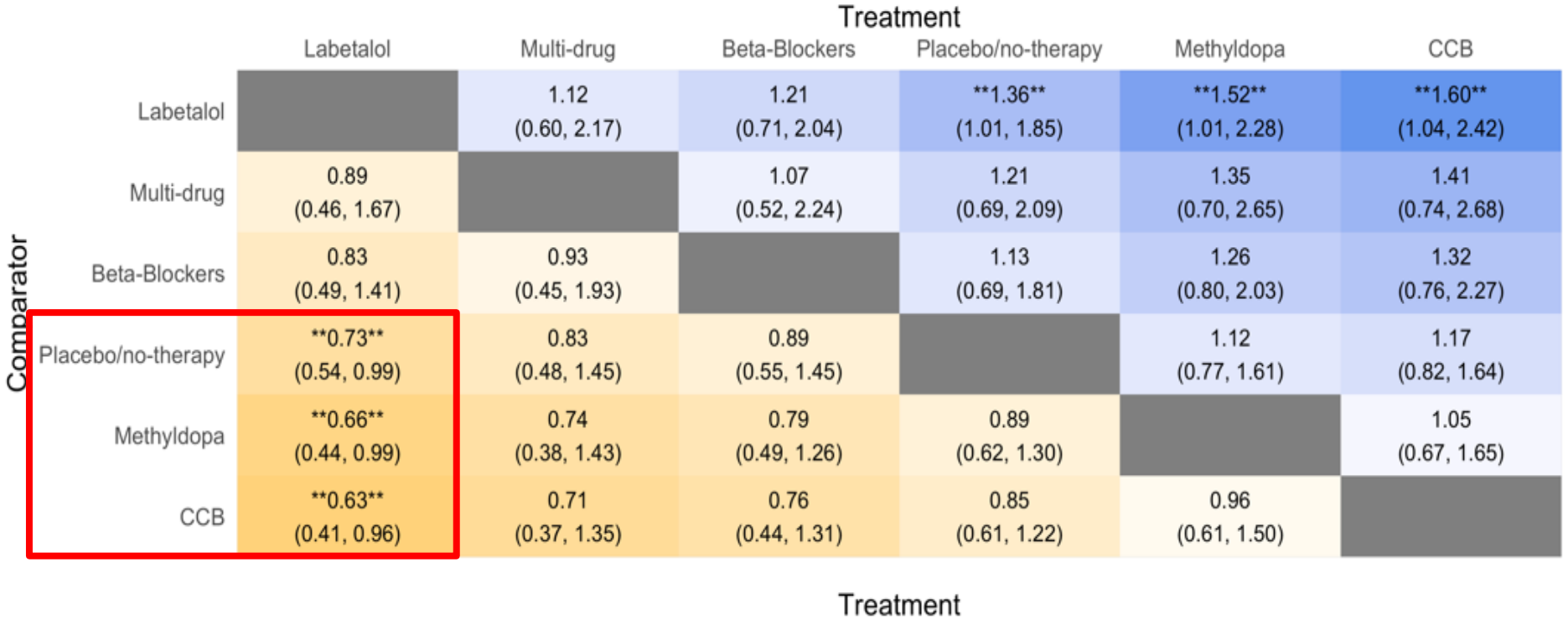
Hypertension 2022 Mar;79(3):614-628



- **Most commonly-studied antihypertensives are better than placebo/no therapy**
- **Labetalol may be better than methyldopa**

Network meta-analysis (N=32 trials, 4662 women)

Proteinuria/pre-eclampsia (median 14%, IQR 8-21%)

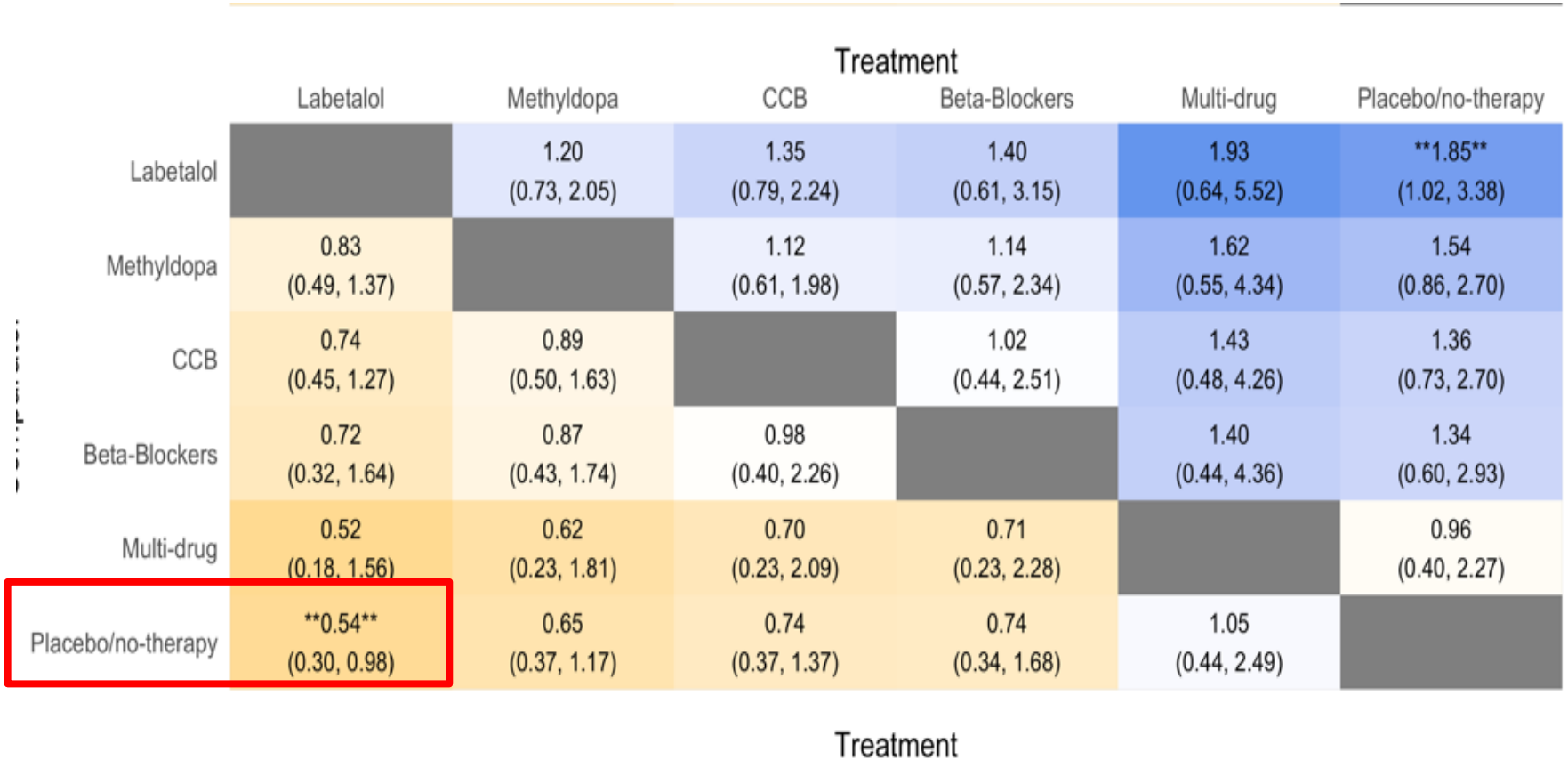


Comparator \ Treatment	Labetalol	Multi-drug	Beta-Blockers	Placebo/no-therapy	Methyldopa	CCB
Labetalol		1.12 (0.60, 2.17)	1.21 (0.71, 2.04)	**1.36** (1.01, 1.85)	**1.52** (1.01, 2.28)	**1.60** (1.04, 2.42)
Multi-drug	0.89 (0.46, 1.67)		1.07 (0.52, 2.24)	1.21 (0.69, 2.09)	1.35 (0.70, 2.65)	1.41 (0.74, 2.68)
Beta-Blockers	0.83 (0.49, 1.41)	0.93 (0.45, 1.93)		1.13 (0.69, 1.81)	1.26 (0.80, 2.03)	1.32 (0.76, 2.27)
Placebo/no-therapy	**0.73** (0.54, 0.99)	0.83 (0.48, 1.45)	0.89 (0.55, 1.45)		1.12 (0.77, 1.61)	1.17 (0.82, 1.64)
Methyldopa	**0.66** (0.44, 0.99)	0.74 (0.38, 1.43)	0.79 (0.49, 1.26)	0.89 (0.62, 1.30)		1.05 (0.67, 1.65)
CCB	**0.63** (0.41, 0.96)	0.71 (0.37, 1.35)	0.76 (0.44, 1.31)	0.85 (0.61, 1.22)	0.96 (0.61, 1.50)	

- **Labetalol may be associated with a reduction in proteinuria/pre-eclampsia, vs. placebo/no therapy, methyldopa or calcium channel blockers**

Network meta-analysis (N=44 trials, 5051 women)

Perinatal death (median 3%, IQR 0-6%)



- **Labetalol may be associated with a reduction in perinatal death**

Network meta-analysis - conclusions

- **All commonly-prescribed antihypertensives are more effective than placebo/no therapy in reducing the risk of severe hypertension**
- **Labetalol may also decrease proteinuria/pre-eclampsia and perinatal death, but we made many comparisons that risked finding significant results by chance alone**
- **No differences in birthweight <10th centile, preterm birth, or neonatal intensive care unit admission**
- **Are ongoing trials of specific comparisons (e.g., UK Giant PANDA trial of oral nifedipine vs. oral labetalol for hypertension, regardless of severity)**

Antihypertensive therapy

Initial therapy should be monotherapy from first-line drugs based on small RCTs: eg, oral labetalol, oral methyldopa, long-acting oral nifedipine, or other oral β-blockers (acebutolol, metoprolol, pindolol, and propranolol) [Abalos 2018]

Choice of agent should be based on characteristics of the patient, contraindications to a particular drug, and physician and patient preference

Additional antihypertensive drugs be used if target BP levels are not achieved with standard-dose monotherapy

Add-on drugs should be from a different drug class chosen from first-line or second-line options [Buttalia 2018]

Antihypertensive titration for non-severe hypertension

[*Preg Hypertens* 2022;27:148-169]

International Society for the Study of Hypertension in Pregnancy

Table 7

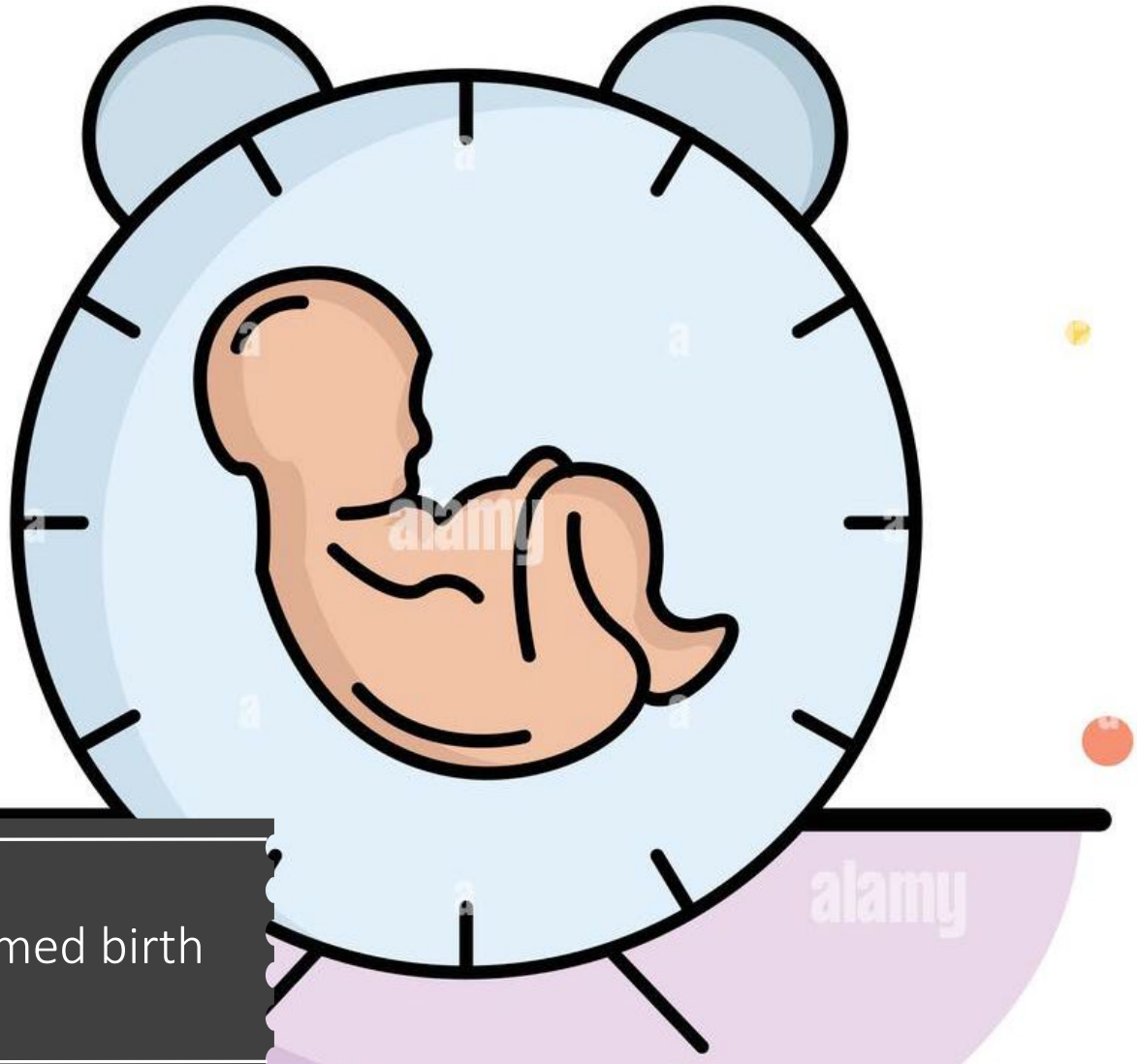
Maintenance therapy and suggested dose titration of antihypertensive therapy for non-urgent control of hypertension in pregnancy (modified from Magee *et al* 2020) [147].

		DOSAGE (mg)						
		Low *	If BP not controlled	**Medium**	If BP not controlled on medium dosage	**High†**		**Maximum**
FIRST-LINE	**CAUTION**		Proceed to medium dose of same low-dose medication		Consider ADDING another low-dose medication rather than going to a high dose of the same medication(s), for a maximum of 3 medications			
Labetalol	▪ Contraindicated with poorly-controlled asthma ▪ May cause neonatal bradycardia and hypoglycaemia and warrants newborn screening	100 mg three to four times/day	→	200 mg three to four times/day		300 mg three to four times/day	→	1200 mg/day
Nifedpine PA or MR	▪ Contraindicated with aortic stenosis	10 mg two to three times/day	→	20 mg two to three times/day		30 mg two to three times/day	→	120 mg/day
Nifedipine XL or LA		30 mg once/day	→	30 mg two times/day *or* 60 mg once/day		30 mg each morning and 60 each evening	→	120 mg/day
Methyldopa	▪ May cause maternal depression	250 mg three to four times/day	→	500 mg three to four times/day		750 mg three times/day	→	2250 mg/day

LA (long-acting), MR (modified release), PA (prolonged action), XL (extended release).

* Starting doses are higher than generally recommended for adults given more rapid clearance in pregnancy.

† When a medication is at high (or maximum) dosage, consider using a different medication to treat any severe hypertension that may develop).



Timed birth

WILL

When to Induce Labour to Limit risk in pregnancy hypertension – a multicentre, randomised controlled trial

FUNDER : National Institute Health Research (NIHR) and Health Technology Assessment (HTA) programme

CHIEF INVESTIGATOR : Professor Laura A. Magee

SPONSORS: King's College London and Guys & St Thomas' NHS Foundation Trust

IRAS 252294 (protocol v4.0)
ISRCTN 77258279

OK to ask

NHS National Institute for Health Research

FUNDED BY NIHR | National Institute for Health Research

UNIVERSITY OF BIRMINGHAM | BCTU Birmingham Clinical Trials Unit

NHS Guy's and St Thomas' NHS Foundation Trust

KING'S College LONDON

Background

- WILL (UK) aimed to address optimal timing of birth for women with chronic or gestational hypertension who reach term gestational age and are well
- Observational data suggest early term birth (at 37-38 weeks) may reduce maternal complications, Caesareans, and stillbirths [Hutcheon BJOG 2011; Cruz AJOG 2012; Ram Obstet Gynecol 2018], as well as costs, related primarily to shorter duration of maternal-fetal surveillance [Vijgen SM BJOG 2010], but neonatal morbidity may increase
- Limited data from subgroups of RCTs suggest similar benefits [Bernardes UOG 2019]
- Inclusion: age ≥16 yrs, chronic or gestational hypertension, singleton, live fetus, 36^{+0}-37^{+6} weeks' gestation, and able to give documented informed consent
- Exclusion: contraindication to either trial arm (e.g., pre-eclampsia), BP≥160/110mmHg until controlled, major fetal anomaly anticipated to require neonatal care unit admission, or participation in another timing of birth trial
- Randomisation (1:1 ratio, minimised for key prognostic variables: site, hypertension type, and prior Caesarean) to 'planned early term birth at 38^{+0-3} weeks' or 'usual care at term' (revised from 'expectant care until at least 40^{+0} weeks', Aug 2022)
- Maternal co-primary: composite of 'poor maternal outcome' (severe hypertension, maternal death, or maternal morbidity)
- Neonatal co-primary: neonatal care unit admission for ≥4 hours
  - Each measured to primary hospital discharge or 28d post-birth (whichever earlier)
- Key secondary: Caesarean

Details of unpublished trial data shared during the presentation cannot be circulated until trial publication.

Conclusions

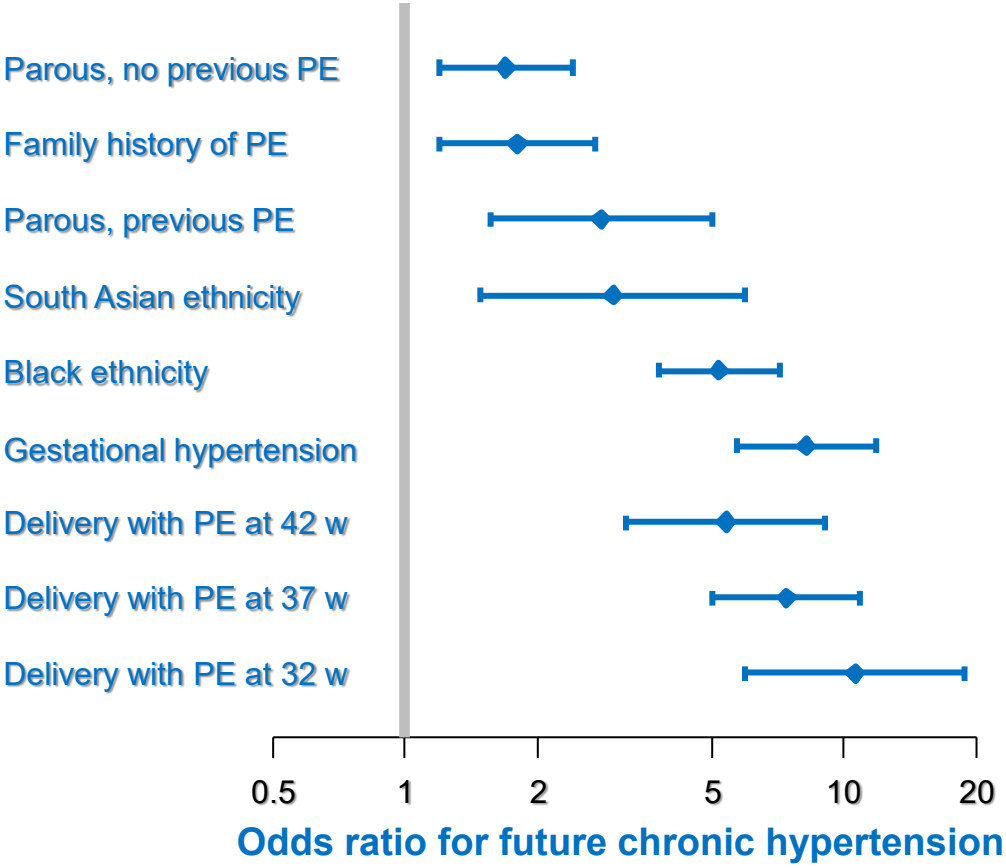
- Over the two-week gestational age window from 38^{+0} to 40^{+0} weeks' gestation, planned early term birth at 38^{+0-3} weeks' gestation (vs. ongoing expectant ['usual']care)
  - Does not decrease a composite of 'poor maternal outcome' or increase neonatal morbidity
  - Is associated with fewer cases of pre-eclampsia and less surveillance
  - Caesarean rates and costs move in the same favourable direction associated with intervention
  - Regardless of the approach taken, at least two-thirds of women will require labour induction, and women are equally satisfied with their care
- Not planning to pursue funding to extend the trial

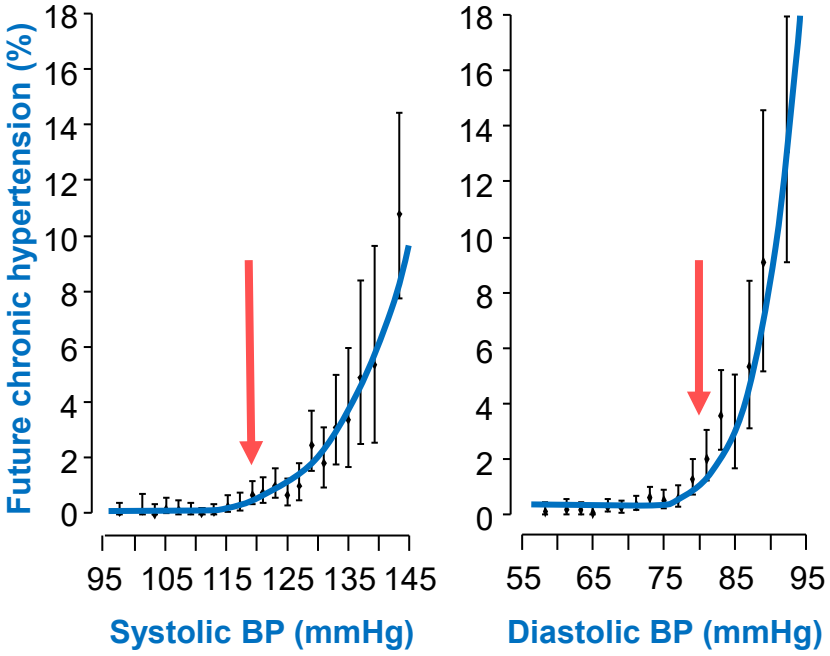
Postpartum

- **Causes 35% of all deaths in women worldwide**
- **Yet, CVD in women is Understudied, Under-recognised, underdiagnosed, and undertreated**
- **Women are under-represented in clinical trials [Lancet 2021;397:2385-438]**
- **Largest contributing risk factor is elevated sBP (PAF 29% among women) [NEJM 2023;389:14]**

- Objective was to develop a predictive model to identify women at increased risk for chronic hypertension based on information collected in the index pregnancy
- Advantage: To focus on CV risk factors that largely account for association between pre-eclampsia/gestational hypertension and CV risk and disease
- Also, these would be stable to future prevention of pre-eclampsia or gestational hypertension
- Cohort of 26,511 women without chronic hypertension, seen in consecutive pregnancies, with mean interpregnancy interval of 3.0 [1.6-5.0] years
- Future chronic hypertension: systolic BP ≥140mmHg or diastolic BP ≥90mmHg, at least twice, 4 hours apart or on 2 consecutive outpatient visits, and documented before pregnancy or < 20 weeks' gestation
- Covariates for modelling
  - Maternal characteristics and medical history
  - Early pregnancy BP
  - Index pregnancy outcome

Results


Parous, no previous PE
Family history of PE
Parous, previous PE
South Asian ethnicity
Black ethnicity
Gestational hypertension
Delivery with PE at 42 w
Delivery with PE at 37 w
Delivery with PE at 32 w
0.5
1
2
5
10
20
Odds ratio for future chronic hypertension


Future chronic hypertension (%)
0
2
4
6
8
10
12
14
16
18
95
105
115
125
135
145
Systolic BP (mmHg)
55
65
75
85
95
Diastolic BP (mmHg)

Performance of screening in pregnancy

Method of screening	N women; DR at 5.9% SPR	N women; DR at 10% SPR	AUROC (95% CI)
PE or GH alone	52.1 (45.2-58.9)	Not applicable	Not applicable
Multivariable model			
Maternal characteristics	39.1 (32.5-45.9)	47.9 (41.1 - 54.8)	(0.77-0.84)
+ BP in early pregnancy	54.0 (47.0-60.8)	67.9 (61.2 - 74.1)	(0.88-0.92)
+ PE or GH	59.5 (52.6-66.2)	68.4 (61.7 - 74.5)	(0.86-0.91)
+ BP in early pregnancy + PE or GH	67.0 (60.3-73.2)	73.5 (67.1 - 79.3)	(0.91-0.94)*

- A model that includes early pregnancy maternal characteristics and BP performs similarly to development of PE or GH for the prediction of future chronic hypertension

Main points

- Treat hypertension from a 140/90mmHg threshold
- For severe hypertension, trend towards use of oral agents
- For non-severe hypertension, antihypertensives titrated to a target diastolic BP of 85mmHg are better for mother without increasing risk to baby
- While there is a wide choice of antihypertensive agents, labetalol may have some advantages over others
- When necessary to achieve BP control, consider adding a second agent, before proceeding to maximum doses of the first agent
- In a BP control era, for women with chronic or gestational hypertension, timed birth at 38^{+0-3} weeks may be best [WILL trial]
- Postpartum, identifying women at risk of chronic hypertension is best undertaken using early pregnancy risk factors that will remain stable targets for CV disease prevention, as efforts to prevent pre-eclampsia achieve success

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