

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Magee LA, von Dadelszen P, Rey E, et al. Less-tight versus tight control of hypertension in pregnancy. *N Engl J Med* 2015;372:407-17. DOI: 10.1056/NEJMoa1404595

SUPPLEMENTARY APPENDIX

| Table/figure | Title | Page |
|--------------|--|------|
| Table S1 | CHIPS Study Group | 2 |
| Figure S1 | CHIPS Trial interventions of less tight and tight control | 11 |
| Figure S2 | Perinatal and maternal outcomes according to 'clinically reasonable' adherence | 13 |
| Figure S3 | Forest plots of outcome according to subgroup analyses | 14 |
| Table S2 | Adherence assessment | 16 |
| Table S3 | Definitions of the primary, secondary, and other outcomes | 18 |
| Table S4 | Reasons why women who were eligible for CHIPS were not enrolled | 24 |
| Table S5 | Detailed baseline characteristics | 25 |
| Table S6 | Antihypertensive therapy and co-interventions | 31 |
| Table S7 | Labour and delivery outcomes | 37 |
| Table S8 | Detailed perinatal outcomes | 38 |
| Table S9 | Detailed maternal outcomes | 46 |
| Table S10 | Interactions between treatment and prognostic factors on outcomes | 50 |

Table S1: CHIPS Study Group

| |
|---|
| <p><u>Steering Committee:</u> Laura A. Magee (Chair), Elizabeth Asztalos, Amiram Gafni, Andrée Gruslin, Michael Helewa, Eileen Hutton, Shoo Lee, Alexander Logan, Jennifer Menzies, Jean-Marie Moutquin, Kellie Murphy, Evelyne Rey, Sue Ross, Johanna Sanchez, Joel Singer, Peter von Dadelszen</p> |
| <p><u>Working Group:</u> Laura A. Magee (Chair), Elizabeth Asztalos, Peter von Dadelszen, Trinh Hoac, Joanne Kirton, Jennifer Menzies, Sue Ross, Johanna Sanchez, Katherine Trigiani, Ainy Zahid</p> |
| <p><u>Adjudication Committee:</u> Laura A. Magee (Chair), Elizabeth Asztalos, Kellie Murphy, Evelyne Rey, Peter von Dadelszen</p> |
| <p><u>Data Safety Monitoring Board:</u> Michael B. Bracken (Chair), Patricia Crowley, Lelia Duley, Richard Ehrenkranz, Kevin Thorpe</p> |
| <p><u>Data programmers and analysts:</u> Sunny Chan, Michael Shi, Shelley Yu</p> |
| <p><u>Collaborators:</u> The number of women recruited in each country and centre is specified in brackets.</p> |
| <p>ARGENTINA (36):</p> |
| <p>Hospital LC Lagomaggiore, Mendoza (16): Raquel de Lourdes Martin, Maria Florencia Bassi, Mirta Clara Caruso, Valeria Lagunas, Fernando Vera</p> |
| <p>Hospital Avellaneda, Tucuman (10): Maria Mohedano de Duhalde, Alicia Beatriz Roque, Patricia Roldan, Esteban Marcos Duhalde, Viviana Dip</p> |
| <p>Hospital JR Vidal, Corrientes (8): Jesus Daniel Aguirre, Elba Mirta Alicia Morales, Griselda Itati Abreo, Teresa De Sagastizabal, Carolina Gomez, Nadia Rizzi</p> |

| |
|--|
| Hospital JM Cullen , Santa Fe (2): Carlos Arias, Ricardo Antonio Bruno |
| AUSTRALIA (85): |
| Ipswich Hospital , Ipswich (36): Kassam Mahomed, Alison Drew, Ann Green, Jane Hoare |
| Women's and Children's Hospital , Adelaide (18): Bill Hague, Suzette Coat, Caroline Crowther, Peter Muller , Sophie Trenowden |
| King Edward Memorial Hospital , Subiaco (17): Barry Walters, Claire Parker, Dorothy Graham, Craig Pennell, Eileen Sung |
| Campbelltown Hospital , Penrith South (8): Angela Makris, Gaksoo Lee, Charlene Thornton, Annemarie Hennessy |
| Liverpool Hospital , Penrith South (5): Angela Makris, Gaksoo Lee, Charlene Thornton, Annemarie Hennessy |
| St John of God Hospital , Subiaco (1): Louise Farrell, Claire Parker, Eileen Sung, Barry Walters |
| BRAZIL (19): |
| Maternidade de Vila Nova Cachoeirinha , Sao Paulo (7): Nelson Sass, Henri Korkes, Dayana Couto Ferreira |
| Hospital Universitario Antonio Pedro , Niteroi (6): Renato Augusto Moreira de Sa, Monique Schmidt Marques Abreu |
| Maternidade Escola da UFRJ , Rio de Janeiro (4): Rita Guerios Bornia, Nancy Ribeiro da Silva, Fernanda Freitas Oliveira Cardoso |
| Hospital Sao Lucas - PUCRS , Porto Alegre (2): Caio Coelho Marques, Jorge Hornos, Ricardo Leal Davdt, Letícia Germany Paula, Pedro Luis Zanella |

| |
|--|
| CANADA (233): |
| British Columbia Women's Hospital and Health Centre, Vancouver (32): Laura A. Magee, Peter von Dadelszen, Gabrielle Inglis, Ruth Dillon, Ashley Docherty, Anna Hutfield |
| Jim Pattison Outpatient Care and Surgery Centre, Surrey (26): Keith Still, Sayrin Lalji, Tamara Van Tent, Chris Hotz, Tracy Messmer |
| St Michael's Hospital, Toronto (22): Joel G. Ray, Howard Berger, Leanne De Souza, Andrea Lausman, Tatiana Freire-Lizama, Kate Besel |
| Foothills Medical Centre, Calgary (21): Paul Gibson, Greta Ellsworth, Leslie Miller, T. Lee-Ann Hawkins |
| Sunnybrook Health Sciences Centre, Toronto (19): Michelle Hladunewich, Anna Rogowsky, Dini Hui, Virginia Collins |
| IWK Health Centre, Halifax (19): Isabelle Delisle, Cora Fanning |
| Royal Alexandra Hospital, Edmonton (16): Nestor Demianczuk, Rshmi Khurana, Winnie Sia, Catherine Marnoch, Carmen Young, Cheryl Lux |
| CHU Sainte-Justine, Montreal (15): Evelyne Rey, Sophie Perreault, Valerie Tremblay |
| CHUS Fleurimont, Sherbrooke (13): Jean-Marie Moutquin, Sophie Desindes, Anne-Marie Côté, Veronique Dagenais |
| Ottawa Hospital Civic Division, Ottawa (13): Andrée Gruslin, Heather Clark, Elaine O'Shea, Ruth Rennicks White |
| Mount Sinai Hospital, Toronto (8): Shital Gandhi, Mary-Jean Martin, Cheryl Brush, Gareth Seaward |

| |
|--|
| Royal University Hospital, Saskatoon (6): Jill Newstead-Angel, Judy Brandt, Jocelyne Martel, Kristine Mytopher, Elise Buschau |
| Ottawa Hospital General Division, Ottawa (5): Andree Gruslin, Erin Keely, Patti Waddell, Ruth Rennicks White, Svetlana Shachkina, Alan Karovitch |
| St Paul's Hospital, Vancouver (5): Robert Anderson, Nicole Koenig, Theresa Yong |
| Toronto East General Hospital, Toronto (5): Marie Vasiliou, Peri Johnson, Beth Allan |
| London Health Sciences Centre, London (4): Renato Natale, Laura Kennedy |
| Royal Victoria Hospital, Montreal (2): Lucie Opatrny, Lorraine Lavigne |
| Regina General Hospital, Regina (1): George Carson, Sheila Kelly |
| Women's Health Centre, St John's (1): Joan Crane, Donna Hutchens |
| CHILE (57): |
| Hospital Dr Sotero del Rio, Puente Alto (45): Juan Pedro Kusanovic, Christian Figueroa, Karla Silva Neculman, Juan Andres Ortiz, Paula Vargas |
| Hospital Base Osorno, Osorno (12): Pedro Ferrand, Jorge Carrillo |
| COLOMBIA (36): |
| Corporacion Comfenalco Valle - Universidad Libre (20), Clinica Versalles (11), Clinica Materno Infantil Farallones (5), Cali: Rodrigo Cifuentes Borrero, Dahiana Marcela Gallo, Luisa Fernanda Moreno |
| ESTONIA (19): |
| Tartu University Hospital - Women's Clinic, Tartu (19): Fred Kirss, Kristiina Rull, Anne Kirss |
| HUNGARY (5): |

| |
|--|
| University of Debrecen , Debrecen (5): Tamas Major, Andrea Fodor, Tunde Bartha |
| ISRAEL (12): |
| Hillel Yaffe Medical Center , Hadera (6): Mordechai Hallak, Nardin Aslih, Saja Anabousi-Murra, Ester Pri-Or |
| Ma'ayney Hayeshua Medical Center , Bnei Brak (3): Linda Harel, Sima Siev |
| Nazareth Hospital (EMMS) , Nazareth (3): Marwan Hakim, Christina Simona Khoury, Najla Hamati |
| JORDAN (13): |
| Islamic Hospital , Amman (13): Mazen El-Zibdeh, Lama Yousef |
| NEW ZEALAND (17): |
| Christchurch Women's Hospital , Christchurch (16): Ruth Hughes, Di Leishman, Barbra Pullar |
| Waitemata Health-North Shore Hospital , Auckland (1): Matthew Farrant |
| POLAND (21): |
| Medical University of Gdansk , Gdansk (9): Malgorzata Swiatkowska-Freund, Krzysztof Preis, Anette Aleksandra Traczyk-Los, Anna Partyka, Joanna Preis-Orlikowska, Mariusz Lukaszuk |
| Polish Mothers Memorial Hospital , Lodz (9): Grzegorz Krasomski, Michael Krekora, Anna Kedzierska-Markowicz, Katarzyna Zych-Krekora |
| University School of Medical Sciences , Poznan (3): Grzegorz H. Breborowicz, Anna Dera-Szymanowska |
| THE NETHERLANDS (96): |

| |
|--|
| Academic Medical Center , Amsterdam (28): Wessel Ganzevoort, Jannet Bakker, Joost Akkermans, Anouk Pels |
| OLVG , Amsterdam (13): Eline van den Akker, Sabine Logtenberg |
| UMCU , Utrecht (10): Steven Koenen, Maartje de Reus, David Borman, Martijn A. Oudijk |
| VU Medical Center , Amsterdam (9): Annemiek Bolte, Viki Verfaillie, Bart Graaf |
| Maxima Medical Centre , Veldhoven (8): Martina Porath, Corine Verhoeven, Ben Willem Mol |
| UMCG , Groningen (6): Maureen T.M. Franssen, Lida Ulkeman, Ineke Hamming, Jose H.M. Keurentjes, Ina van der Wal |
| Isala Klinieken Zwolle , Zwolle (5): S.W.A. Nij Bijvank, A.A. Lutjes |
| Tergooiziekenhuizen , Hilversum (5): Henricus Visser, Jannet Bakker |
| MUMC Maastricht , Maastricht (4): Hubertina Catharina Johanna Scheepers |
| St Antonius Ziekenhuis , Nieuwegein (3): Erik van Beek, David Borman, Coby van Dam, Kathy van den Berg-Swart |
| Kennemer Gasthuis Haarlem , Haarlem (2): Paula Pernet, Birgit van der Goes |
| Diakonessen Ziekenhuis , Utrecht (1): Nico Schuitemaker |
| Flevo ziekenhuis , Almere (1): Gunilla Kleiverda, Marcel van Alphen, Ageeth Rosman |
| Jeroen Bosch Hospital , 's-Hertogenbosch (1): Ingrid Gaugler-Senden, Marieke Linders |
| UNITED KINGDOM (268): |
| Guy's & St Thomas' Hospital , London (38): Catherine Nelson-Piercy, Annette Briley, May Ching Soh, Kate Harding, Hayley Tarft |
| New Cross Hospital , Wolverhampton (31): David Churchill, Katherine Cheshire, Julia Icke, |

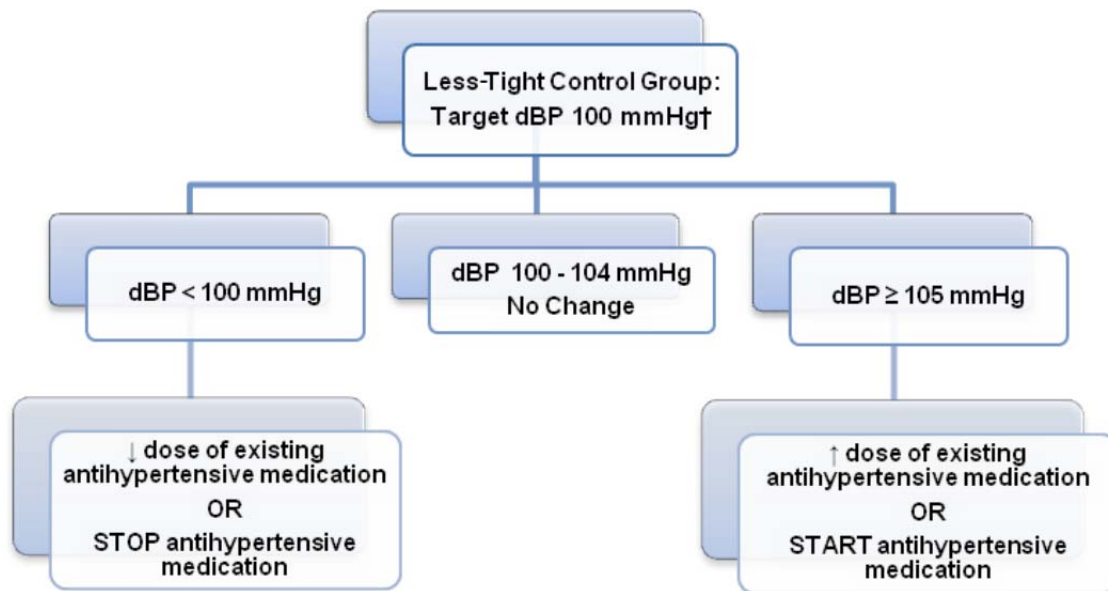
| |
|---|
| Mausumi Ghosh |
| Nottingham City Hospital , Nottingham (30): James Thornton, Yvonne Toomassi, Karen Barker, Joanne Fisher, Nicky Grace, Amanda Green, Joanne Gower , Anna Molnar, Shobhana Parameshwaran, Andrew Simm |
| Queen's Medical Centre , Nottingham (22): James Thornton, George Bugg, Yvette Davis, Ruta Desphande, Yvette Gunn, Mohammed Houda, Anna Molnar, Nia Jones |
| Royal Victoria Infirmary , Newcastle upon Tyne (22): Jason Waugh, Carly Allan, Gareth Waring |
| Liverpool Women's Hospital , Liverpool (16): Steve A. Walkinshaw , Angela Pascall, Mark Clement-Jones, Michelle Dower, Gillian Houghton, Heather Longworth, Tej Purewal |
| Bradford Royal Infirmary , Bradford (13): Derek Tuffnell, Diane Farrar, Jennifer Syson, Gillian Butterfield, Vicky Jones, Rebecca Palethorpe, Tracey Germaine |
| Leicester Royal Infirmary , Leicester (12): Marwan Habiba, Debbie Lee |
| Wexham Park Hospital , Slough (12): Olufemi Eniola, Lynne Blake, Jane Khan |
| City Hospitals Sunderland NHS Foundation Trust , Sunderland (10): Helen M. Cameron, Kim Hinshaw, Amanda Bargh, Eileen Walton |
| South Warwickshire NHS Trust , Warwick (9): Olanrewaju Sorinola, Anna Guy, Zoe D'Souza, Rhiannon Gabriel, Jo Williams |
| Derriford Hospital , Plymouth (8): Ross Welch, Heidi Hollands |
| York Hospital , York (8): Olujimi Jibodu, Sara Collier, Pauline Tottie, Claire Oxby, James Dwyer |

| |
|--|
| Singleton Hospital , Swansea (7): Franz Majoko, Helen Goldring, Sharon Jones |
| Chesterfield Royal Hospital , Chesterfield (6): Janet Cresswell , Louise Underwood, Mary Kelly-Baxter, Rebecca Robinson |
| Sheffield Teaching Hospitals NHS Foundation Trust , Sheffield (6): Dilly Anumba, Anne Chamberlain, Clare Pye |
| St Mary's Hospital , Manchester (6): Clare Tower , Sue Woods, Lisa Horrocks, Fiona Prichard, Lynsey Moorhead, Sarah Lee, Louise Stephens , Cara Taylor, Suzanne Thomas, Melissa Whitworth, Jenny Myers |
| Birmingham Women's Hospital , Birmingham (5): Ellen Knox, Katie Freitas, Mark Kilby, Amanda Cotterill |
| Lancashire Teaching Hospitals NHS Foundation Trust , Lancashire (3): Khalil Abdo, Katrina Rigby, Julie Butler, Fiona Crosfill, Sean Hughes, Sanjeev Prashar, Fatimah Soydemir |
| The Royal Derby Hospital , Derby (3): Janet Ashworth, Lorraine Mycock, Jill Smith |
| Basildon & Thurrock University Hospital , Basildon (1): Amaju Ikomi , Kerry Goodsell, Jean Byrne, Maxwell Masuku, Alice Pilcher |
| USA (70): |
| Cooper University Hospital , Camden (13): Meena Khandelwal, Gunda Simpkins, Michelle Iavicoli, Yon Sook Kim, Richard Fischer, Robin Perry |
| Medical University of South Carolina , Charleston (11): Eugene Y. Chang, Tamara D. Saunders, Betty W. Oswald, Kristin D. Zaks |
| Beth Israel Deaconess , Boston (8): Sarosh Rana, Dawn McCullough |

| |
|--|
| Yale-New Haven Hospital , New Haven (8): Anna Sfakianaki, Cheryl Danton, Erin Kustan, Luisa Coraluzzi |
| Norton Hospital Downtown (7), Norton Suburban Hospital (2) , Louisville: Helen How, Christina Waldon |
| East Carolina University , Greenville (6): Jeffrey Livingston, Sherry Jackson, Lisa Greene |
| Meriter Hospital , Madison (6): Dinesh Shah |
| Oregon Health & Science University , Portland (5): Jorge E. Tolosa, Monica Rincon, Leonardo Pereira, Amy E. Lawrence, Janice E. Snyder |
| University of North Carolina , Chapel Hill (4): D. Michael Armstrong, Teresa Blue, Austin Hester, Kathryn Salisbury |

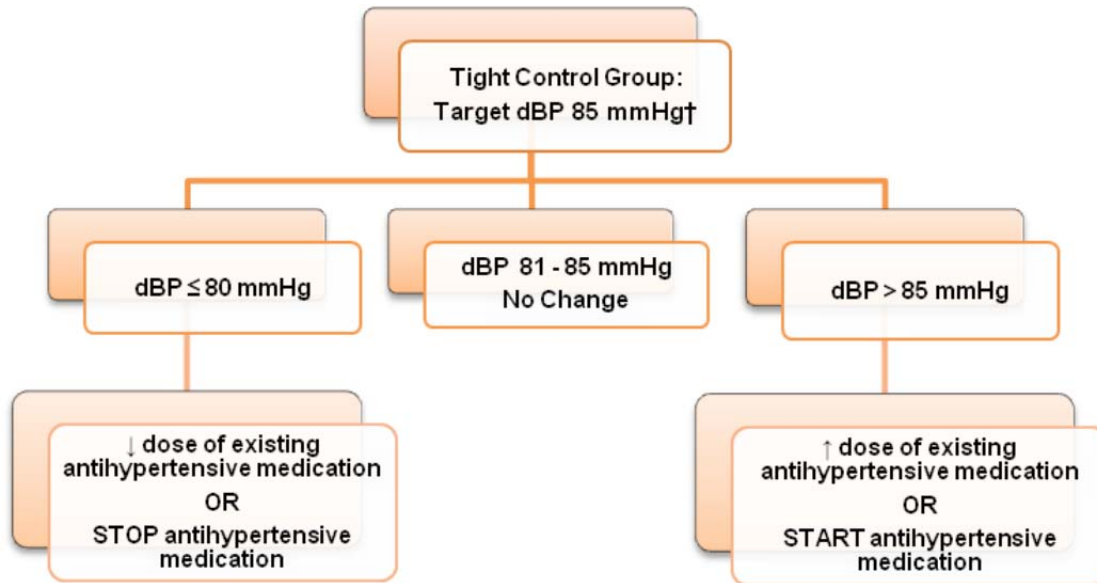
Figure S1: CHIPS interventions

Figure S1A – Less-tight control of dBP: target diastolic blood pressure (dBP) and appropriate responses to it with regards to antihypertensive therapy



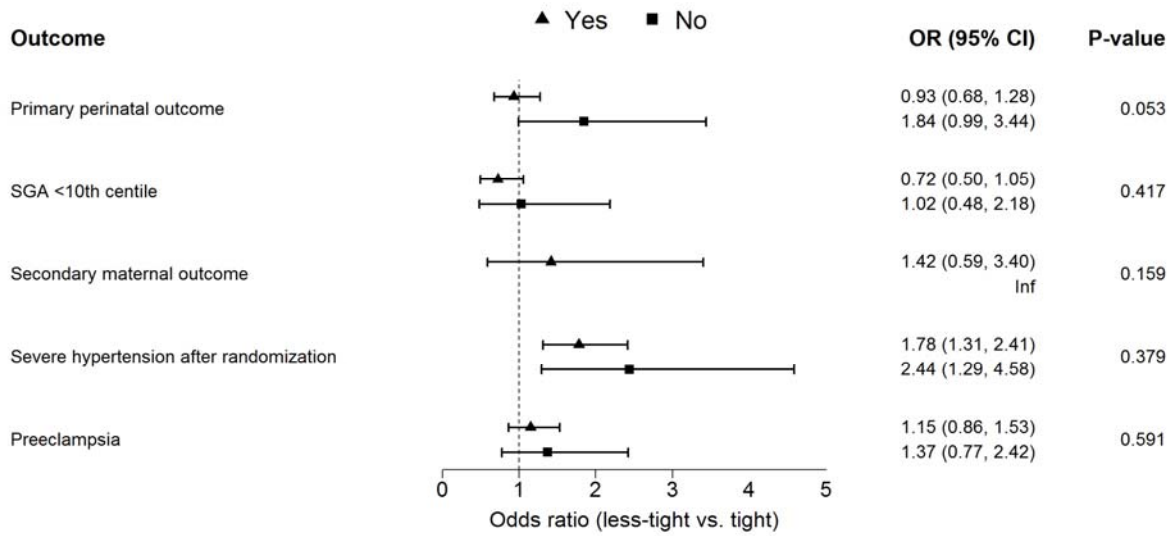
† If sBP ≥ 160 mm Hg, increase dose of existing medication or start new antihypertensive medication to get sBP < 160 mm Hg.

Figure S1B: Tight control of dBP: target diastolic blood pressure (dBP) and appropriate responses to it with regards to antihypertensive therapy



† If sBP ≥ 160 mm Hg, increase dose of existing medication or start new antihypertensive medication to get sBP < 160 mm Hg.

Figure S2: Perinatal and maternal outcomes according to ‘clinically reasonable’ adherence (see Table S2 for definition)*

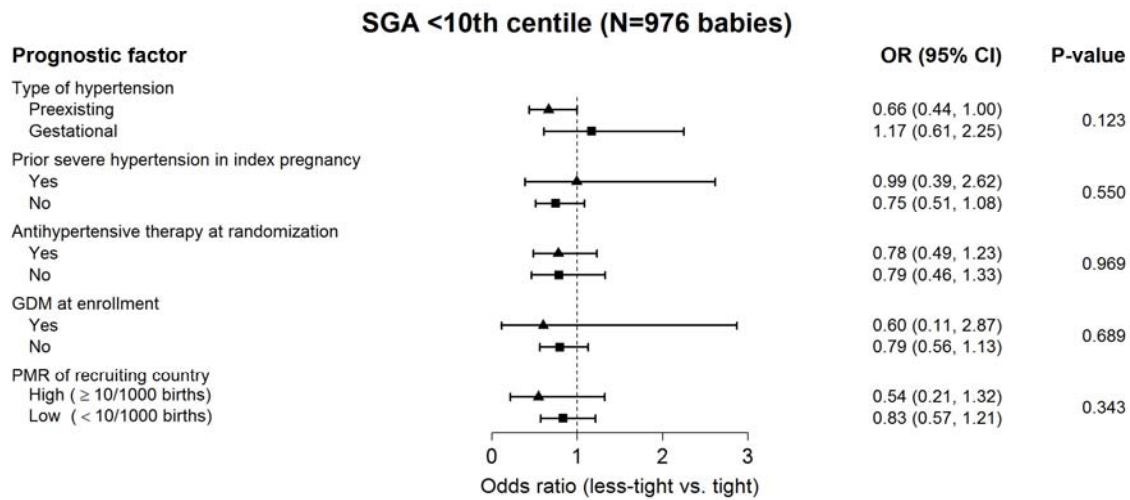
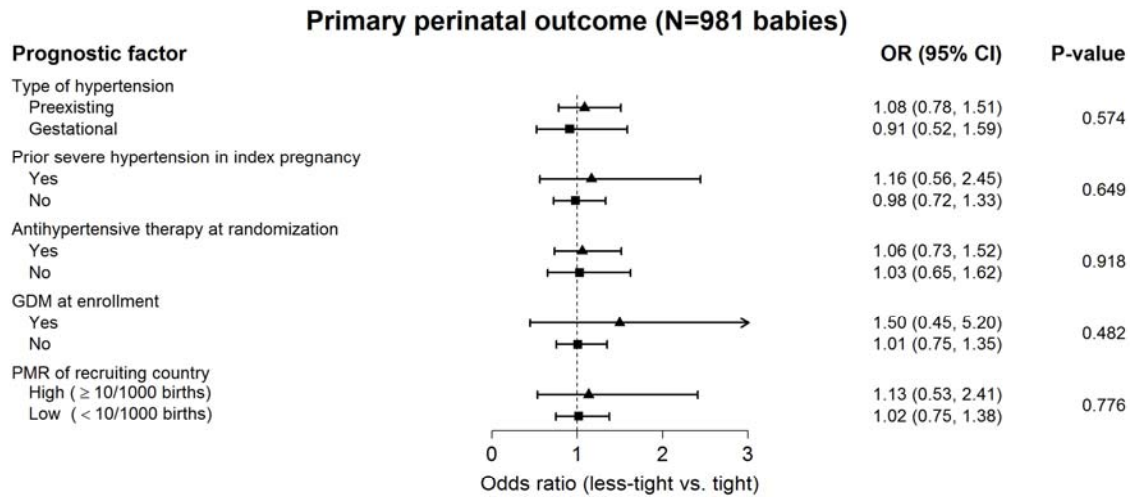


CI (confidence interval), OR (odds ratio), SGA (small for gestational age)

* Comparisons of OR and 95% CI for less tight vs. tight control were made using the Breslow-Day test of homogeneity.

Figure S3: Forest plots of outcome according to subgroup analyses

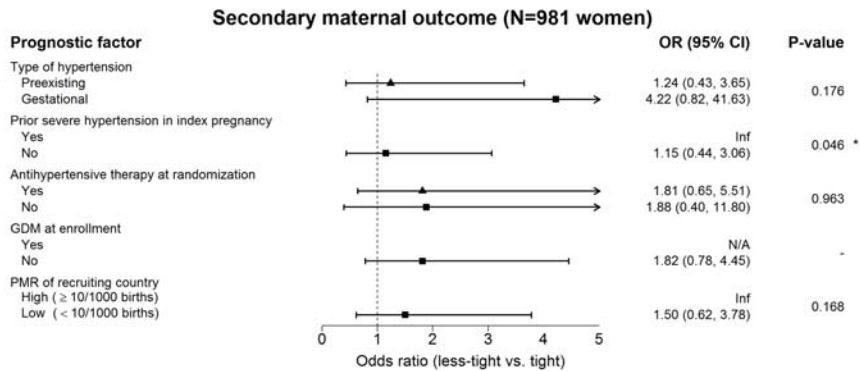
Figure S3A: Subgroup analyses for perinatal outcomes*



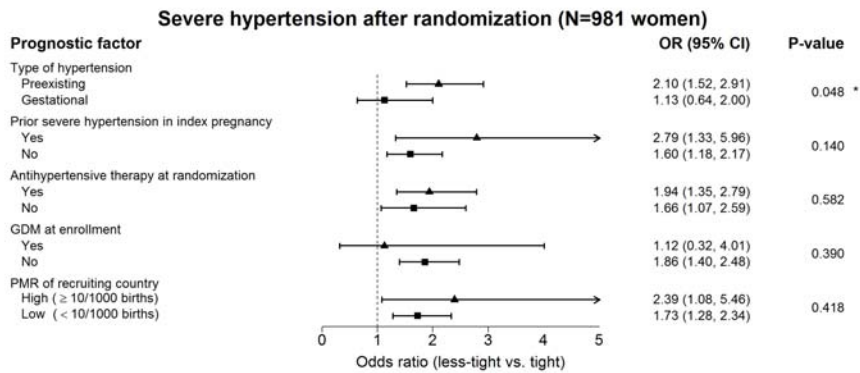
CI (confidence interval), GDM (gestational diabetes mellitus), OR (odds ratio), PMR (perinatal mortality ratio), SGA (small for gestational age)

* Comparisons of OR and 95% CI for less tight vs. tight control were made using the Breslow-Day test of homogeneity.

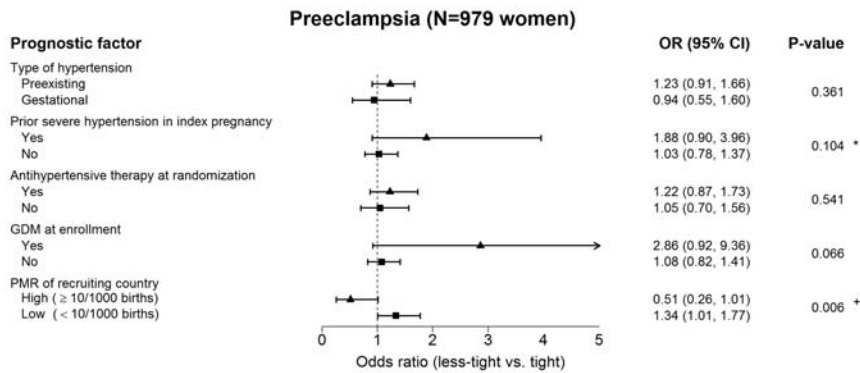
Figure S3B: Subgroup analyses for maternal outcomes†



* This interaction was of marginal statistical significance. It was likely due to chance because if prior severe hypertension were truly an adverse prognostic factor, the rates of the secondary maternal outcome should have been higher in the less-tight and tight control groups, compared with those without prior severe hypertension



* This interaction was of marginal statistical significance. It was likely due to chance because if preexisting hypertension were truly an adverse prognostic factor, the rates of severe hypertension should have been higher in the less-tight and tight control groups, compared with those without gestational hypertension.



* This interaction was of potential significance. There appeared to be more preeclampsia with less-tight than tight control in the prior severe hypertension subgroup, but not in the no prior severe hypertension subgroup; an interaction term was included in the adjusted regression.

† This interaction is of potential significance and will require further exploration.

CI (confidence interval), GDM (gestational diabetes mellitus), OR (odds ratio), PMR (perinatal mortality ratio), SGA (small for gestational age)

‡ Comparisons of OR and 95% CI for less tight vs. tight control were made using the Breslow-Day test of homogeneity.

Table S2: Adherence assessment

Table S2A: For less tight control (target dBP of 100mmHg)

| Strict adherence | | | | |
|--|--------------------------------------|---------------------------------|----------------|---|
| dBP (mmHg) | Drug decreased or stopped | No change | | Drug increased or new drug started |
| | | NOT on meds at visit | On meds | |
| <100 | Adherence | Adherence | X | X |
| 100-104 | X | Adherence | Adherence | X |
| ≥105 | X | X | X | Adherence |
| 'Clinically reasonable' adherence | | | | |
| dBP (mmHg) | Drug decreased or stopped | No change | | Drug increased or new drug started |
| | | NOT on meds at visit | On meds | |
| ≤95 | Adherence | Adherence | X | X |
| 96-99 | Adherence | Adherence | Adherence | X |
| 100-104 | X | Adherence | Adherence | X |
| ≥105 | X | X | X | Adherence |

Table S2B: For tight control (target dBP 85mmHg)

| Strict adherence | | | | |
|--|--------------------------------------|---------------------------------|----------------|---|
| dBP (mmHg) | Drug decreased or stopped | No change | | Drug increased or new drug started |
| | | NOT on meds at visit | On meds | |
| ≤80 | Adherence | Adherence | X | X |
| 81-85 | X | Adherence | Adherence | X |
| >85 | X | X | X | Adherence |
| 'Clinically reasonable' adherence | | | | |
| dBP (mmHg) | Drug decreased or stopped | No change | | Drug increased or new drug started |
| | | NOT on meds at visit | On meds | |
| ≤80 | Adherence | Adherence | X | X |
| 81-85 | Y | Adherence | Adherence | X |
| 86-89 | Y | Adherence | Adherence | Adherence |
| ≥90 | Y | Y | Y | Adherence |

For BOTH groups:

If sBP ≥160mmHg at any time, the only compliant action is to increase antihypertensive medication or start new drug.

Table S3: Definitions of the primary, secondary, and other CHIPS outcomes

| Outcome | Definition |
|--|---|
| Primary perinatal outcome: pregnancy loss or high level neonatal care for >48hr (until primary discharge home or 28d of life, whichever was later) | |
| Pregnancy loss | |
| Elective termination | With reason specified, including static fetal growth |
| Miscarriage | Death of a fetus <500g or <20 wks |
| Ectopic pregnancy | Pregnancy outside the uterine cavity |
| Stillbirth | Death of a fetus ≥500g or ≥20 wks |
| Neonatal death | |
| High level neonatal care for >48 hr | Defined as greater-than-normal newborn care |
| Secondary maternal outcome: one/more serious maternal complications (including death) (until primary discharge home or 6 wks postpartum, whichever was later) | |
| Maternal death | |
| Stroke | Acute neurological event with deficits lasting > 24 hr, not due to a post-ictal state |
| Eclampsia | Generalized convulsion in the absence of a history of epilepsy |

| Outcome | Definition |
|-----------------------------|---|
| Blindness | Either retinal or cortical, defined as loss of visual acuity in the presence of intact pupillary response to light |
| Uncontrolled hypertension | Need for a third parenteral antihypertensive agent (hypertension requiring administration of 3 or more different parenteral [intravenous or intramuscular] antihypertensive agents within a 12 hour period) |
| Inotropic support | Use of vasopressors to keep sBP > 90 mm Hg or a MAP > 70 mm Hg |
| Pulmonary oedema | Diagnosed clinically with one/more of oxygen saturation < 95%, diuretic treatment or x-ray confirmation |
| Respiratory failure | Intubation, ventilation (either by ETT or non-invasively), or need for > 50% oxygen for > 1 hr which is not due to Cesarean delivery |
| Myocardial ischemia or MI | By characteristic ECG changes and markers of myocardial necrosis |
| Hepatic dysfunction | INR>1.2 in the absence of DIC or treatment with warfarin, OR, in the presence of DIC or treatment with warfarin: either mixed hyperbilirubinemia >1.0 mg/dL (or >17 µM) or hypoglycemia <45 mg/dL (<2.5 mM) in the absence of insulin |
| Hepatic hematoma or rupture | Presence of a blood collection under the hepatic capsule as confirmed by imaging or at laparotomy |

| Outcome | Definition |
|----------------|---|
| Renal failure | Serum creatinine >200 µM |
| Transfusion | Of any blood product |
| Other | As detailed, with appropriate information from hospital records |

Other perinatal outcomes

Serious neonatal complications

| | |
|-------------------------------------|---|
| Severe respiratory distress | Requiring assisted ventilation for ≥24hr beginning within the first 72 hr of life |
| ‘Early-onset’ sepsis | Within first 48 hr of life, confirmed by positive blood or cerebrospinal fluid cultures |
| Respiratory distress syndrome (RDS) | Assisted ventilation and supplemental oxygen within the 1 st 24 hr of life, for ≥24 hr AND either X-ray compatible with RDS or surfactant given within the 1 st 24 hr of life |
| Bronchopulmonary dysplasia | For infants born at <32 wk, supplemental oxygen for a chronic pulmonary disorder at a corrected gestational age of 36 wk |
| Severe retinopathy of prematurity | Stage 4 or 5 in one/both eyes (intraretinal ridge with extraretinal fibrovascular proliferation, or retinal detachment, respectively) by worst stage in the most severely affected eye at 4 wk |
| Central nervous | |

| Outcome | Definition |
|--|---|
| system morbidity | |
| <i>Intraventricular hemorrhage (IVH)</i> | Either ventricular enlargement with/without a germinal matrix or IVH, by cranial imaging/autopsy in the first 2 wk of life OR parenchymal echodensities/lucencies in the white or gray matter on one/more brain imaging studies/autopsy done after 21 d of life |
| <i>Cystic periventricular leukomalacia</i> | Periventricular cystic changes in white matter, excluding subependymal and choroid plexus cysts, by cranial ultrasound, CT, MRI or at autopsy |
| <i>Hypoxic-ischemic encephalopathy</i> | For infants born at ≥ 35 wk who have moderate-severe encephalopathy (clinical seizures or ≥ 3 of: lethargy, decreased spontaneous activity, distal flexion/full extension, focal/general hypotonia, weak/absent suck or incomplete Moro primitive reflexes, and autonomic system abnormalities {constricted/dilated/deviated/unresponsive pupils, bradycardia or variable heart rate, or periodic breathing/apnea}) AND ≥ 2 of 10 min Apgar < 5 , cord or postnatal ABG pH < 7.0 within 1 hr of birth, cord or postnatal ABG base deficit ($> 16 \mu\text{M}$), or need for any ventilation from birth for ≥ 10 min |
| <i>Parenchymal</i> | Yes/no |

| Outcome | Definition |
|--------------------------------------|---|
| <i>hemorrhage</i> | |
| Necrotizing enterocolitis | Perforation of the intestine, pneumatosis intestinalis or air in the portal vein, diagnosed by x-ray, surgery, or autopsy |
| Other maternal outcomes | |
| Severe hypertension | sBP \geq 160 mm Hg or dBP \geq 110 mm Hg |
| Proteinuria | Yes/no according to \geq 2+ by urinary dipstick, \geq 30 mg/mmol urinary creatinine by spot testing, elevated urinary albumin:creatinine ratio according to local criteria, or \geq 0.3 g/d by 24 hr urine collection |
| Preeclampsia | New proteinuria or one/more preeclampsia symptoms, signs, and/or abnormal laboratory tests |
| Symptoms | Headache, visual disturbances, persistent right upper quadrant or epigastric pain, severe nausea or vomiting, chest pain, dyspnea |
| Signs | In addition to severe hypertension: eclampsia, placental abruption, or pulmonary edema |
| Abnormal maternal laboratory testing | Elevated aspartate or alanine aminotransferase or lactate dehydrogenase (according to local laboratory criteria) with symptoms, platelet count $< 100,000 \times 10^9/L$, or serum creatinine > 2.26 mg/dL ($> 200 \mu M$) |

CT (computed tomography), DIC (disseminated intravascular coagulation), ETT (endotracheal

tube), INR (*international normalised ratio*), MAP (*mean arterial pressure*), MI (*myocardial infarction*), MRI (*magnetic resonance imaging*), sBP (*systolic BP*)

Table S4: Reasons why 385 women (of 881 women identified as eligible for CHIPS) were not enrolled at 45 (47.9%) sites that reported on eligible women identified

| | N=385 women |
|--|--------------------|
| Woman did not want to participate | 340 (88.3%) |
| Woman didn't want to be randomized or be a study subject | 140 |
| Woman didn't want additional demands on her time | 65 |
| Woman didn't want her BP to be higher than normal | 63 |
| Woman did not want to take drugs during pregnancy | 52 |
| 'Other' | 88 |
| Woman's maternity care provider did not want woman to participate | 38 (9.9%) |
| Didn't want woman to receive less tight control | 11 |
| Had medical reasons | 9 |
| Didn't want additional demands on the woman's time | 7 |
| Didn't want woman to receive tight control | 5 |
| Didn't want her to be randomized or be a study subject | 3 |
| 'Other' | 13 |
| CHIPS co-ordinator was unavailable to recruit | 9 (2.3%) |
| Woman was lost to follow-up | 9 (2.3%) |

‡ More than one reason may apply.

Table S5: Detailed baseline characteristics at enrollment

| Characteristic | Less-tight control† (N=497) | Tight control (N=490) |
|---|--|--------------------------------------|
| Maternal age at EDD (yr) | 34.0±5.7 | 33.7±5.8 |
| Mother's self-declared ethnicity | | |
| Caucasian | 298 (60.0%) | 315 (64.3%) |
| Black | 62 (12.5%) | 61 (12.4%) |
| Asian | 62 (12.5%) | 46 (9.4%) |
| Hispanic | 58 (11.7%) | 63 (12.9%) |
| Other | 17 (3.4%) | 5 (1.0%) |
| Prepregnancy or first weight in pregnancy (kg) | 81.0 [68.0; 95.0] 4 missing | 80.0 [67.0; 96.0] 3 missing |
| BMI (kg/m²) | 30.9±7.4 4 missing | 31.2±7.7 5 missing |

| Characteristic | Less-tight control† (N=497) | Tight control (N=490) |
|--|--|--------------------------------------|
| Underweight (<18.5) | 1 (0.2%) | 2 (0.4%) |
| Normal weight (18.5-24.9) | 116 (23.3%) | 112(22.9%) |
| Overweight (25.0-29.9) | 131 (26.4) | 135 (27.6%) |
| Obese class I (30.0-34.9) | 109 (21.9%) | 109 (22.2%) |
| Obese class II (35.0-35.9) | 83 (16.7%) | 68 (13.9%) |
| Obese class III (≥40.0) | 53 (10.7%) | 59 (12.0%) |
| Cigarette smoking during this pregnancy | 35 (7.0%) | 28 (5.7%) |
| Nulliparous | 161(32.4%) | 168 (34.3%) |
| Conceived through use of ARF | 20 (4.0%) | 23 (4.7%) |
| Gestational age (wks) | 23.7±6.3 (23 wks + 5 d) | 24.2±6.3 (24 wks + 1 d) |
| 14 ⁺⁰ -20 ⁺⁶ | 186 (37.4%) | 164 (33.5%) |
| 21 ⁺⁰ -28 ⁺⁶ | 160 (32.2%) | 164 (33.5%) |

| Characteristic | Less-tight control† (N=497) | Tight control (N=490) |
|---|-----------------------------------|-----------------------------|
| 29 ⁺⁰ -33 ⁺⁶ | 151 (30.4%) | 162 (33.1%) |
| N women recruited at ≥22 wks after time of detailed anatomy scan ‡ | 294 (59.2%) | 311 (63.5%) |
| Type of non-proteinuric hypertension ¶ | | |
| Preexisting hypertension | 371 (74.6%) | 365 (74.5%) |
| Gestational hypertension | 126 (25.4%) | 125 (25.5%) |
| Prior sBP≥160 or dBP≥110 mm Hg in this pregnancy | 82 (16.5%) | 59 (12.0%) |
| On antihypertensive treatment at enrolment | 279 (56.1%) | 287 (58.6%) |
| Taking one agent | 245 (87.8%) | 257 (89.5%) |
| Taking two or more agents | 34 (12.2%) | 30 (10.5%) |
| Agents taken | | |
| <i>Labetalol</i> | 124 (44.4%) | 135 (47.0%) |
| <i>Methyldopa</i> | 139 (49.8%) | 125 (43.6%) |

| Characteristic | Less-tight control† (N=497) | Tight control (N=490) |
|---|-----------------------------------|-----------------------------|
| | <i>Nifedipine</i> | 34 (12.2%) |
| | <i>Other‡</i> | 43 (15.0%) |
| | | 14 (4.9%) |
| BP (mmHg) within one week before randomization | | |
| Systolic BP§ | 140.4±9.7 | 139.7±9.8 |
| Diastolic BP¶ | 92.6±4.8 | 92.2±5.2 |
| Currently using home BP monitoring | 185 (37.2%) | 194 (39.6%) |
| Gestational diabetes (at enrolment) | 32 (6.4%) | 31 (6.3%) |
| Other medication at enrolment | | |
| Aspirin | 127 (25.6%) | 130 (26.5%) |
| Folic acid and/or prenatal vitamin | 328 (66.0%) | 313 (63.9%) |
| | <i>1 missing</i> | |
| PMR of recruiting country | | |
| High (≥10/1000 births) # | 80 (16.1%) | 81 (16.5%) |

| Characteristic | Less-tight control† (N=497) | Tight control (N=490) |
|---|--------------------------------|--------------------------|
| Low (<10/1000 births) | 417 (83.9%) | 409 (83.5%) |
| Regions where women were recruited | | |
| Australasia (N=8 sites) | 52 (10.5%) | 50 (10.2%) |
| Middle East (N=4 sites) | 12 (2.4%) | 13 (2.7%) |
| North America (N=29 sites) | 152 (30.6%) | 151 (30.8%) |
| South America (N=13 sites) | 74 (14.9%) | 74 (15.1%) |
| UK and Europe (N=40 sites) | 207 (41.6%) | 202 (41.2%) |

ARF (artificial reproductive technology), BMI (body mass index), BP (blood pressure), EDD (expected date of delivery), PMR (perinatal mortality ratio)

Mean (SD), median [interquartile range], or N (%) women unless otherwise stated.

† One woman had a contraindication to less-tight control (cardiomyopathy), but she remained in the Trial.

‡ Of these women, 3 were subsequently identified as having a baby with a congenital anomaly. 1 in the less-tight group with (bilateral polycystic kidney disease) and 2 in the tight control group (congenital heart disease, of which one had been identified prior to randomization. All remained in the Trial.

¶ 1 (0.2%) woman in less-tight and 1 (0.2%) in tight control actually had proteinuria at randomization and were randomized in error; they remained in the Trial. 5 women in less-tight and 3 in tight control were randomized based on the wrong hypertension stratum due to incorrect identification of the type of hypertension at that time.

∫ Other antihypertensive agents included other calcium channel blockers (7 women in less-tight vs. 7 in tight), atenolol (1 vs. 3, respectively), other beta-blockers (5 vs. 1, respectively), hydralazine (2 vs. 1, respectively), diuretics (1 vs. 0, respectively), other alpha-blockers (0 vs. 1, respectively), angiotensin receptor blocker (1 vs. 0, respectively), and ketanserin (0 vs. 1, respectively).

§ There were 7 women (5 in less-tight vs. 2 in tight) who had sBP ≥ 160 mmHg. Their ineligibility was identified after randomization. They remained in the Trial.

†† There were 12 women (4 in less-tight vs. 7 in tight) whose dBp did not meet eligibility criteria, because dBp was < 90 mmHg on no antihypertensive medication (1 vs. 0, respectively), dBp was < 85 mmHg while taking antihypertensive therapy (3 vs. 6, respectively), or dBp was ≥ 106 mmHg (1 vs. 1, respectively). All such women continued in the Trial.

‡ The 4 countries with high PMR were Argentina (N=4 sites), Chile (N=2), Jordan (N=1), Brazil (N=4), and Colombia (N=3).

Table S6: Maternal management and maternal/fetal surveillance after randomization and before delivery

| | Less-tight control N=497 women | Tight control N=489 women | Adjusted OR [95% CI] |
|--|---|------------------------------------|-------------------------|
| BP measurement | | | |
| Type of measurement device used at first office/clinic visit | | | |
| <i>Automated</i> | 140 (29.0%) | 121 (25.5%) | 1.49 [0.95,2.34] |
| <i>Aneuroid</i> | 241 (49.5%) | 249 (52.5%) | 0.71 [0.47,1.07] |
| <i>Mercury</i> | 103 (21.1%) | 102 (21.5%) | 1.03 [0.62,1.69] |
| Oral antihypertensive therapy † | | | |
| | 379 (76.9%) ^{***} | 458 (93.9%) ^{***} | 0.18 [0.12,0.29] |
| Antepartum | 362 (73.4%) ^{***} | 452 (92.6%) ^{***} | 0.17 [0.11,0.27] |

| | Less-tight control N=497 women | Tight control N=489 women | Adjusted OR [95% CI] |
|---------------------------------|---|--|---------------------------------|
| Postpartum | 323 (65.5%) ^{***} | 382 (78.3%) ^{***} | 0.51 [0.38,0.68] |
| Took one agent antepartum | 209/362 (57.7%) | 281/452 (62.2%) | |
| Took two/more agents antepartum | 153/362 (42.3%) | 171/452 (37.8%) | |
| Agents used antenatally ¶ | | | |
| Labetalol | 242/362 (66.9%) | 304/452 (67.3%) | |
| Methyldopa | 154/362 (42.5%) | 182/452 (40.3%) | |
| Nifedipine | 115/362 (31.8%) | 136/452 (30.1%) | |
| Other † | 52/362 (14.4%) | 55/452 (12.2%) | |

| | Less-tight control N=497 women | Tight control N=489 women | Adjusted OR [95% CI] |
|--|---|------------------------------------|-------------------------|
| Co-interventions | | | |
| Mothers decreased activity level (one or more methods) [¶] | 306 (61.6%) 1 missing | 321 (65.6%) 2 missing | 0.81 [0.61,1.08] |
| Quit work outside the home | 165 (53.9%) | 174 (54.2%) | |
| Bedrest at home | 88 (28.8%) | 105 (32.7%) | |
| Avoided strenuous activity inside home | 138 (45.1%) | 155 (48.3%) | |
| Admission to hospital | 49 (16.0%) | 54 (16.8%) | |
| Other [§] | 44 (14.4%) | 44 (13.7%) | |
| Other medications taken | | | |
| Folic acid and/or a prenatal vitamin antenatally | 348 (70.0%) 2 missing | 335 (68.5%) 2 missing | 1.09 [0.78,1.51] |
| Aspirin antenatally | 153 (30.8%) 1 missing | 162 (33.1%) 2 missing | 0.82 [0.59,1.14] |
| Antenatal corticosteroids | | | |

| | Less-tight control N=497 women | Tight control N=489 women | Adjusted OR [95% CI] |
|---|---|------------------------------------|-------------------------|
| <i>For fetal lung maturation ‡</i> | 121 (24.5%) | 124 (25.4%) | 0.92 [0.67,1.25] |
| <i>For other reasons ‡ ††</i> | 8 (1.6%) | 7 (1.4%) | 1.14 [0.41,3.21] |
| Magnesium sulphate † | 87 (17.6%) | 73 (15.0%) | 1.20 [0.84,1.72] |
| Maternal monitoring (N women) | | | |
| N women using home BP monitoring | 231 (46.5%) 1 missing | 225 (46.0%) 2 missing | 1.02 [0.73,1.41] |
| Blood or urine tests at the laboratory | 461 (92.8%) | 451 (92.2%) | 1.06 [0.65,1.74] |
| Office/clinic visits | 487 (98.0%) | 474 (96.9%) | 1.71 [0.72,4.06] |
| Seen in obstetric day unit in relevant centres (of N women seen in relevant | 182/319 (57.1%) | 182/320 (56.9%) | 1.10 [0.75,1.62] |

| | Less-tight control N=497 women | Tight control N=489 women | Adjusted OR [95% CI] |
|---|---|------------------------------------|-------------------------|
| sites) | | | |
| Enrolled in antepartum home care in relevant centres (N women seen in relevant sites) | 109/364 (29.9%) 1 missing | 105/358 (29.3%) | 1.02 [0.66,1.59] |
| Seen in emergency room (N women) † | 199 (40.0%) 1 missing | 178 (36.4%) | 1.21 [0.91,1.61] |
| One/more antenatal admissions (not including delivery admission) (N women) | 133 (26.8%) 3 missing | 122 (24.9%) 1 missing | 1.05 [0.78,1.42] |
| <i>N admissions</i> | 172 | 155 | |
| Fetal surveillance | | | |
| Non-stress tests or cardiotocographs (N woman) | 362 (72.8%) 1 missing | 357 (73.0%) | 0.98 [0.71,1.36] |
| Fetal ultrasounds (N women) | 460 (92.6%) | 455 (93.0%) | 0.86 [0.52,1.43] |

Mean (SD), median [interquartile range], or N (%) women unless otherwise stated.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ (level of significance set for ‘other’ outcomes in CHIPS)

† All sites reported use of automated devices that required operators.

‡ These data were not available for 2 women in the less-tight control group and 1 woman in the tight control group who were lost to follow-up for delivery, as well as 2 women in the less-tight control group and 1 woman in the tight control group who withdrew. (see Consort Diagram, Figure S1).

¶ Responses are not mutually exclusive.

∫ Other antihypertensive agents included hydralazine (24 women in less-tight vs. 24 in tight), other calcium channel blockers (9 vs. 18, respectively), other beta-blockers (8 vs. 4, respectively), diuretics (9 vs. 0, respectively), other alpha-blockers (5 vs. 4, respectively), ketanserin (4 vs. 3, respectively), atenolol (1 vs. 3, respectively), or a natural antihypertensive supplement (0 vs. 1, respectively). Post-randomization use of atenolol was a protocol violation.

§ Other changes in activity were decreased work hours (5 women in less-tight vs. 9 in tight), decreased exercise (11 vs. 10, respectively), rested more (22 vs. 25, respectively), rested more with specific mention of illness/injury/pain (4 vs. 7, respectively), and decreased driving (3 vs. 1, respectively).

†† Other indications for corticosteroids included: HELLP syndrome (5 women in less-tight vs. 1 in tight), asthma (0 vs. 3, respectively), rheumatic disease (1 vs. 2, respectively), Bell’s palsy (1 vs. 1, respectively), and vomiting (1 vs. 0, respectively).

‡‡ An emergency room was defined as a place where women go to be seen urgently (without an appointment).

Table S7: Labour and delivery outcomes

| | Less-tight control (493 women, 493 fetuses) | Tight control (488 women, 488 fetuses) | Adjusted OR [95% CI] |
|--|--|---|---------------------------------|
| Type of labour | | | |
| Spontaneous | 109 (22.2%) | 104 (21.4%) | 1.06 [0.78,1.44] |
| Induced | 224(45.5%) | 218 (44.9%) | 1.07 [0.82,1.38] |
| No labour (Caesarean prior to labour) | 159 (32.3%) | 164 (33.7%) | 0.89 [0.68,1.18] |
| Cesarean delivery | 231 (47.0%) | 250 (51.4%) | 0.81 [0.63,1.04] |
| Vaginal delivery | 261 (53.0%) | 236 (48.6%) | 1.24 [0.96,1.60] |
| Spontaneous | 234 (89.7%)* | 196 (83.1%)* | |
| Operative | 27 (10.3%)* | 40 (16.9%)* | |
| Sex of fetus/newborn | | | 1.07 [0.83,1.38] |
| Male | 255/492 (51.8%) | 244/486 (50.2%) | |
| Female | 237/492 (48.2%) | 242/486 (49.8%) | |

Mean (SD), median [interquartile range], or N (%) women unless otherwise stated.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ (level of significance set for 'other' outcomes in CHIPS)

Table S8: Detailed perinatal outcomes

| | Less-tight control (493 women, 493 fetuses) | Tight control (488 women, 488 fetuses) | Adjusted OR [95% CI] |
|---|--|---|-------------------------|
| Primary outcome: Pregnancy loss or high level neonatal care for >48hr | 155/493 (31.4%) | 150/488 (30.7%) | 1.02 [0.77,1.35] |
| Pregnancy loss | 15 (3.0%) | 13 (2.7%) | 1.14 [0.53,2.45] |
| Miscarriage | 0 (0.0%) | 1 (0.2%) | |
| Ectopic pregnancy | 0 (0.0%) | 0 (0.0%) | |
| Elective termination † | 1 (0.2%) | 1 (0.2%) | |
| Perinatal death | 14 (2.8%) | 11 (2.3%) | 1.25 [0.56,2.81] |
| Stillbirth | 12 | 7 | |
| Gestational age at delivery (wks) | 27.1 [25.6; 30.4] | 26.6 [22.3; 30.1] | |
| Cause(s) ‡ | | | |
| <i>Placental</i> | 9 | 6 | |

| | Less-tight control (493 women, 493 fetuses) | Tight control (488 women, 488 fetuses) | Adjusted OR [95% CI] |
|---|--|---|-------------------------|
| <i>Congenital anomaly(ies)¶</i> | 2 | 0 | |
| <i>Cord problem</i> | 1 | 1 | |
| Neonatal death | 2 | 4 | |
| Cause(s) | | | |
| <i>Complications of preterm birth</i> | 2 | 3 | |
| <i>Congenital anomaly(ies)§</i> | 0 | 1 | |
| <i>Adequate ventilation not achieved</i> | 1 | 0 | |
| High level neonatal care for >48hr | 141 (29.4%) | 139 (29.0%) | 1.00 [0.75,1.33] |
| § | | | |
| During delivery admission – indication†† | N=133 babies | N=131 babies | |
| <i>Early gestational age</i> | 100/133 (75.2%) | 82/131 (62.6%) | |
| <i>Birth weight (low or high)</i> | 65/133 (48.9%) | 59/131 (45.0%) | |

| | Less-tight control (493 women, 493 fetuses) | Tight control (488 women, 488 fetuses) | Adjusted OR [95% CI] |
|---|--|---|-------------------------|
| <i>Respiratory problems</i> | 66/133 (49.6%) | 49/131 (37.4%) | |
| <i>Sepsis work-up</i> | 26/133 (19.5%) | 29/131 (22.1%) | |
| <i>Hyper- or Hypo-glycemia</i> | 21/133 (15.8%) | 27/131 (20.6%) | |
| <i>Low Apgar score</i> | 14/133 (10.5%) | 13/131 (9.9%) | |
| <i>Other †</i> | 22/133 (16.5%) | 30/131 (22.9%) | |
| Gestational age at delivery (wk) | 36.8 ±3.4 (36 wks & 5 d) | 37.1 ±3.1 (37 wks & 1 d) | |
| Delivery at <37wk | 175 (35.6%) | 153 (31.5%) | 1.18 [0.90,1.56] |
| Delivery at <34wk | 77 (15.7%) | 61 (12.6%) | 1.23 [0.85,1.77] |
| Birth weight (g) | 2998 [2235;3451] | 2993 [2390;3430] | |
| <2500g | 148 (30.1%) | 136 (28.0%) | 1.10 [0.83,1.46] |
| <1250g | 33 (6.7%) | 28 (5.8%) | 1.14 [0.67,1.94] |
| SGA newborns ¶¶ | | | |

| | Less-tight control (493 women, 493 fetuses) | Tight control (488 women, 488 fetuses) | Adjusted OR [95% CI] |
|--|--|---|-------------------------|
| Birth weight < 10 th centile | 79 (16.1%) | 96 (19.8%) | 0.78 [0.56,1.08] |
| Birth weight < 3 rd centile | 23 (4.7%) | 26 (5.3%) | 0.92 [0.51,1.63] |
| Other perinatal outcomes of liveborns | N=480 | N=479 | |
| Apgar score <7 at 5 minutes | 19 (4.0%) | 24 (5.0%) | 0.82 [0.44,1.55] |
| Cord or neonatal arterial/venous gas | 281 (58.5%) | 267 (55.7%) | 1.23 [0.91,1.67] |
| pH <7.0 | 2 | 6 | |
| Base deficit >16mEq/L (>16mM) | 2 | 5 | |
| | 1 missing | | |
| Neonatal morbidity among liveborns | | | |
| Respiratory morbidity | | | |
| Clinical respiratory problem ff | 82 (17.1%) | 67 (14.0%) | 1.19 [0.83,1.71] |

| | Less-tight control (493 women, 493 fetuses) | Tight control (488 women, 488 fetuses) | Adjusted OR [95% CI] |
|--|--|---|-------------------------|
| <i>Due to RDS</i> | 52 | 45 | |
| <i>Due to TTN</i> | 19 | 16 | |
| <i>Due to other reasons §§</i> | 24 | 17 | |
| Oxygen beyond the first 10 min of life | 34 (7.1%) 1 missing | 25 (5.2%) 2 missing | 1.24 [0.72,2.14] |
| Ventilatory support (± intubation) beyond the first 10 min of life | 35 (7.3%) 2 missing | 38 (7.9%) | 0.86 [0.53,1.40] |
| Surfactant used | 28 (5.8%) | 26 (5.4%) | 0.97 [0.55,1.69] |
| Patent ductus arteriosus | 10 (2.1%) | 6 (1.3%) | 1.64 [0.58,4.63] |
| Major operation(s) performed ††† | 4 (0.8%) | 4 (0.8%) | |
| One/more serious neonatal complications | 40 (8.3%) | 40 (8.4%) | 0.96 [0.60,1.52] |
| Severe respiratory distress | 34 (7.1%) | 34 (7.1%) | 0.94 [0.57,1.55] |

| | Less-tight control (493 women, 493 fetuses) | Tight control (488 women, 488 fetuses) | Adjusted OR [95% CI] |
|--|--|---|-------------------------|
| | 2 missing | | |
| Sepsis within first 48hr of life | 3 (0.6%) | 1 (0.2%) | |
| Bronchopulmonary dysplasia | 9 (1.9%) | 5 (1.0%) | 1.78 [0.59,5.40] |
| Severe retinopathy of prematurity | 0 (0.0%) | 0(0.0%) | |
| Central nervous system morbidity | | | |
| <i>Intraventricular hemorrhage</i> | 7 (1.5%) | 10 (2.1%) | 0.68 [0.25,1.81] |
| | | 1 missing | |
| <i>Cystic periventricular leukomalacia</i> | 0(0.0%) | 1 (0.2%) | |
| <i>Hypoxic-ischemic encephalopathy</i> | 1 (0.2%) | 0(0.0%) | |
| Necrotizing enterocolitis | 3 (0.6%) | 4 (0.8%) | |
| Length of hospital stay (d) | 3.1 [2.0; 7.3] | 3.0 [2.0; 6.0] | |

ABG (arterial blood gas), ECMO (extracorporeal membrane oxygenation), RDS (respiratory distress syndrome), SGA (small for gestational age), TTN (transient tachypnoea of the newborn)

Mean (SD), median [interquartile range], or N (%) women unless otherwise stated.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

† The reasons specified for elective termination were severe preeclampsia (1 in the less-tight, at 22⁺⁰ weeks) and fetal anomaly of Edward's Syndrome (1 in tight control at 23⁺⁴ weeks).

‡ These were determined by masked review of autopsy reports (7 babies in less-tight vs. 3 in tight) or other source documents by the Outcomes Adjudication Committee. The placental causes identified were not mutually exclusive, as follows: preeclampsia (1 in less-tight vs 3 in tight), IUGR (7 vs 4, respectively), abruption (1 vs. 2, respectively), and massive feto-maternal hemorrhage (1 vs. 0, respectively).

¶ The specific anomalies were bilateral polycystic kidney disease and complex congenital heart disease. Neither anomaly was known prior to randomization.

∫ The specific anomaly was congenital heart disease which was not known prior to randomization.

§ Of liveborns admitted to high level neonatal care for >48hr, 4 babies suffered a neonatal death (1 in less-tight vs. 3 in tight).

†† Indications for admission are not mutually exclusive.

‡ Other reasons for high level neonatal care for >48hr were: hypothermia (4 babies in less-tight vs. 5 in tight), metabolic acidosis (3 vs. 7, respectively), low BP (3 vs. 3, respectively), gastrointestinal (2 vs. 2, respectively), jaundice (1 vs. 4, respectively), neurological (4 vs. 2, respectively), cardiac (3 vs. 1, respectively), haematological (0 vs. 3, respectively), and fever/infection (0 vs. 2, respectively), congenital/chromosomal abnormality (1 vs. 1, respectively), and birth trauma (1 vs. 0, respectively).

¶¶ Birth weight centiles were determined for gestational age (22-43 wks) and gender according to Kramer. There were 2 babies born at <22 weeks (2 in less-tight and 0 in tight control) with birth weights 180 and 426 g; they were excluded from the analysis.

∫∫ Not mutually exclusive.

§§ Other causes of clinical respiratory problems were: problem not yet diagnosed (8 babies in less tight vs. 6 in tight), pneumothorax/pneumomediastinum (1 vs. 6, respectively), pneumonia (4 vs. 2, respectively), chronic lung disease (4 vs. 1, respectively), apnoea (4 vs. 1, respectively), meconium aspiration (2 vs. 0, respectively), pulmonary hemorrhage (1 vs. 0, respectively), and cardiac (0 vs. 1, respectively).

†† Major operations performed were laparotomy (2 babies in less-tight vs. 3 in tight) and thoracotomy (2 vs. 1, respectively).

Table S9: Detailed maternal outcomes

| | Less-tight control (N=493 women) | Tight control (N=488 women) | Adjusted OR [95% CI] |
|---|---|------------------------------------|-----------------------------|
| Serious maternal complications (one/more)† ‡ | 18 (3.7%) | 10 (2.0%) | 1.74 [0.79, 3.84] |
| Uncontrolled hypertension | 0 | 0 | |
| TIA/stroke | 0 | 1 | |
| Pulmonary oedema | 2 | 1 | |
| Renal failure | 0 | 1 | |
| Transfusion ¶ | 16 | 8 | |
| Placental abruption | 11 (2.2%) | 11 (2.3%) | 0.94 [0.40, 2.21] |
| Severe hypertension (BP ≥160/110 mm Hg) | 200 (40.6%) ^{***} | 134 (27.5%) ^{***} | 1.80 [1.34, 2.38] |
| Preeclampsia | 241/491 (49.1%) | 223/488 (45.7%) | 1.14 [0.88, 1.47] |
| Defined only by new proteinuria‡ | 148/241 (61.4%) | 132/223 (59.2%) | 1.08 [0.74, 1.59] |
| Defined only by one/more | 93/241 (38.6%) | 91/223 (40.8%) | 0.92 [0.63, 1.36] |

| | Less-tight control (N=493 women) | Tight control (N=488 women) | Adjusted OR [95% CI] |
|--|---|-----------------------------------|-------------------------|
| preeclampsia symptoms, signs, and/or abnormal laboratory tests (without proteinuria) | | | |
| Gestational age at onset (wk) | 32.0±5.1 | 33.0±4.6 | |
| One/more preeclampsia symptoms § | 171/493 (34.7%) | 156/488 (32.0%) | 1.11 [0.84,1.46] |
| Abnormal laboratory tests | | | |
| <i>Platelet count <100x10⁹/L</i> | 21/493 (4.3%)* | 8/488 (1.6%)* | 2.63 [1.15,6.05] |
| <i>Elevated AST or ALT with symptoms</i> | 21/492 (4.3%)* | 9/488 (1.8%)* | 2.33 [1.05,5.16] |
| <i>Elevated LDH with symptoms</i> | 16/491 (3.3%) | 9/488 (1.8%) | 1.78 [0.77,4.11] |
| <i>'HELLP' syndrome ††</i> | 9/493 (1.8%) | 2/488 (0.4%) | 4.35 [0.93,20.35] |
| <i>Serum creatinine >2.26mg/dL (>200µM)</i> | 0 | 1/488 (0.2%) | |
| Maternal length of stay | | | |
| Antenatal, up to and including | 1.0 [1.0; 4.0] | 1.0 [1.0; 4.0] | |

| | Less-tight control (N=493 women) | Tight control (N=488 women) | Adjusted OR [95% CI] |
|--|----------------------------------|-----------------------------|----------------------|
| delivery (d) | | | |
| Postnatal (d) | 3.0 [2.0; 4.0] | 3.0 [2.0; 4.0] | |
| Stay \geq 10d | 12 (2.4%) | 5 (1.0%) | |
| Poorly controlled hypertension as the indication for readmission to hospital before 6 wks postpartum | 12 | 4 | 4.95 [0.73,33.78] |

AST (aspartate aminotransferase), ALT (alanine aminotransferase), HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelet syndrome), LDH (lactate dehydrogenase), PPH (postpartum hemorrhage)

Mean (SD), median [interquartile range], or N (%) women unless otherwise stated.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

† Responses are not mutually exclusive.

‡ No woman died or suffered one of the following complications: eclampsia, blindness, respiratory failure, hepatic haematoma/rupture/dysfunction, myocardial ischaemia/infarction, or required inotropic support.

¶ Antenatal transfusion was received by one woman in tight control (who also received a postnatal transfusion). Postnatal transfusion was for: anemia not otherwise specified (4 women in less-tight vs. 4 in tight), PPH (5 vs. 2, respectively), HELLP syndrome (3 vs. 0, respectively), operative blood loss (3 vs. 0, respectively), and placental abruption (1 vs. 2, respectively).

∫ Proteinuria was determined by the highest amount recorded by whichever method was used.

§ Preeclampsia symptoms were headache (persistent, new, or unusual), visual disturbances, chest pain, dyspnea, severe nausea or vomiting, and/or persistent right upper quadrant or epigastric abdominal pain.

†† 'HELLP' syndrome was defined as platelets $<100 \times 10^9/L$ and either elevated AST or ALT with symptoms or elevated LDH with symptoms.

Table S10: Interactions between treatment and prognostic factors on outcomes

| Prognostic factor and type of DBP control | Primary perinatal outcome (N=981 babies) | | p | | SGA <10 th centile (N=976 babies) | | p | | Secondary maternal outcome (N=981 women) | | p | | Severe hypertension after randomization (N=981 women) | | p | | Preeclampsia (N=979 women) | | p | |
|---|--|--------------------|-------------|--|--|--------------------|-------------|--|--|--------------------|-------------|--|---|--------------------|--------------|--|----------------------------|--------------------|---|-------------|
| | (155/493 in less-tight vs. 150/488 in tight) | | | | | | | | | | | | | | | | | | | |
| | Yes N=305 | No N=676 | | | Yes N=175 | No N=801 | | | Yes N=28 | No N=953 | | | Yes N=334 | No N=647 | | | Yes N=464 | No N=515 | | |
| Type of hypertension | | | 0.57 | | | | 0.12 | | | | 0.18 | | | | 0.048 | | | | | 0.36 |
| Preexisting | | | | | | | | | | | | | | | | | | | | |
| Less-tight | 113/369 (30.6%) | 256/369 (69.4%) | | | 51/366 (13.9%) | 315/366 (86.1%) | | | 10/369 (2.7%) | 359/369 (97.3%) | | | 159/369 (43.1%) | 210/369 (56.9%) | | | 176/368 (47.8%) | 192/368 (52.2%) | | |
| Tight | 105/363 (28.9%) | 258/363 (71.1%) | | | 71/361 (19.7%) | 290/361 (80.3%) | | | 8/363 (2.2%) | 355/363 (97.8%) | | | 96/363 (26.4%) | 267/363 (73.6%) | | | 155/363 (42.7%) | 208/363 (57.3%) | | |
| Gestational | | | | | | | | | | | | | | | | | | | | |
| Less-tight | 42/124 (33.9%) | 82/124 (66.1%) | | | 28/124 (22.6%) | 96/124 (77.4%) | | | 8/124 (6.5%) | 116/124 (93.5%) | | | 41/124 (33.1%) | 83/124 (66.9%) | | | 65/123 (52.8%) | 58/123 (47.2%) | | |

| Prognostic factor and type of DBP control | Primary perinatal outcome (N=981 babies) | | p | SGA <10 th centile (N=976 babies) | | p | Secondary maternal outcome (N=981 women) | | p | Severe hypertension after randomization (N=981 women) | | p | Preeclampsia (N=979 women) | | p |
|--|--|-------------------|------|--|--------------------|------|--|--------------------|------------|---|-------------------|------|---|-------------------|------------|
| | Yes | No | | Yes | No | | Yes | No | | Yes | No | | Yes | No | |
| | (155/493 in less-tight vs. 150/488 in tight) | | | (79/490 in less-tight vs. 96/486 in tight) | | | (18/493 in less-tight vs. 10/488 in tight) | | | (200/493 in less-tight vs. 134/488 in tight) | | | (241/ 491 in less-tight vs. 223/488 in tight) | | |
| | N=305 | N=676 | | N=175 | N=801 | | N=28 | N=953 | | N=334 | N=647 | | N=464 | N=515 | |
| Tight | 45/125 (36.0%) | 80/125 (64.0%) | | 25/125 (20.0%) | 100/125 (80.0%) | | 2/125 (1.6%) | 123/125 (98.4%) | | 38/125 (30.4%) | 87/125 (69.6%) | | 68/125 (54.4%) | 57/125 (45.6%) | |
| Prior severe hypertension in index pregnancy | | | 0.65 | | | 0.55 | | | 0.046 * | | | 0.14 | | | 0.10† ‡ |
| Yes | | | | | | | | | | | | | | | |
| Less-tight | 35/82 (42.7%) | 47/82 (57.3%) | | 15/81 (18.5%) | 66/81 (81.5%) | | 7/82 (8.5%) | 75/82 (91.5%) | | 54/82 (65.8%) | 28/82 (34.2%) | | 53/82 (64.6%) | 29/82 (35.4%) | |
| Tight | 23/59 (39.0%) | 36/59 (61.0%) | | 11/59 (18.6) | 48/59 (81.4%) | | 0 (0%) | 59/59 (100%) | | 24/59 (40.7%) | 35/59 (59.3%) | | 29/59 (49.2%) | 30/59 (50.8%) | |
| No | | | | | | | | | | | | | | | |

| Prognostic factor and type of DBP control | Primary perinatal outcome (N=981 babies) | | p | SGA <10 th centile (N=976 babies) | | p | Secondary maternal outcome (N=981 women) | | p | Severe hypertension after randomization (N=981 women) | | p | Preeclampsia (N=979 women) | | p |
|--|--|--------------------|-------------|--|--------------------|-------------|--|--------------------|-------------|---|--------------------|-------------|---|--------------------|-------------|
| | Yes | No | | Yes | No | | Yes | No | | Yes | No | | Yes | No | |
| | (155/493 in less-tight vs. 150/488 in tight) | | | (79/490 in less-tight vs. 96/486 in tight) | | | (18/493 in less-tight vs. 10/488 in tight) | | | (200/493 in less-tight vs. 134/488 in tight) | | | (241/ 491 in less-tight vs. 223/488 in tight) | | |
| | N=305 | N=676 | | N=175 | N=801 | | N=28 | N=953 | | N=334 | N=647 | | N=464 | N=515 | |
| Less-tight | 120/411 (29.2%) | 291/411 (70.8%) | | 64/409 (15.6%) | 345/409 (84.4%) | | 11/411 (2.7%) | 400/411 (97.3%) | | 146/411 (35.5%) | 265/411 (64.5%) | | 188/409 (46.0%) | 221/409 (54.0%) | |
| Tight | 127/429 (29.6%) | 302/429 (70.4%) | | 85/427 (19.9%) | 342/427 (80.1%) | | 10/429 (2.4%) | 419/429 (97.7%) | | 110/429 (25.6%) | 319/429 (74.4%) | | 194/429 (45.2%) | 235/429 (54.8%) | |
| Antihypertensive therapy at randomization | | | 0.92 | | | 0.97 | | | 0.96 | | | 0.58 | | | 0.54 |
| Yes | | | | | | | | | | | | | | | |
| Less-tight | 97/276 (35.1%) | 179/276 (64.9%) | | 43/274 (15.7%) | 231/274 (84.3%) | | 12/276 (4.3%) | 264/276 (95.7%) | | 122/276 (44.2%) | 154/276 (55.8%) | | 137/275 (49.8%) | 138/275 (50.2%) | |
| Tight | 97/286 (33.9%) | 189/286 (66.1%) | | 55/284 (19.4%) | 229/284 (80.6%) | | 7/286 (2.4%) | 279/286 (97.6%) | | 83/286 (29.0%) | 203/286 (71.0%) | | 128/286 (44.8%) | 158/286 (55.2%) | |

| Prognostic factor and type of DBP control | Primary perinatal outcome (N=981 babies) | | p | SGA <10 th centile (N=976 babies) | | p | Secondary maternal outcome (N=981 women) | | p | Severe hypertension after randomization (N=981 women) | | p | Preeclampsia (N=979 women) | | p |
|---|--|--------------------|-------------|--|--------------------|-------------|--|--------------------|---|---|--------------------|-------------|---|--------------------|-------------|
| | Yes | No | | Yes | No | | Yes | No | | Yes | No | | Yes | No | |
| | (155/493 in less-tight vs. 150/488 in tight) | | | (79/490 in less-tight vs. 96/486 in tight) | | | (18/493 in less-tight vs. 10/488 in tight) | | | (200/493 in less-tight vs. 134/488 in tight) | | | (241/ 491 in less-tight vs. 223/488 in tight) | | |
| | Yes N=305 | No N=676 | | Yes N=175 | No N=801 | | Yes N=28 | No N=953 | | Yes N=334 | No N=647 | | Yes N=464 | No N=515 | |
| No | | | | | | | | | | | | | | | |
| Less-tight | 58/217 (26.7%) | 159/217 (73.3%) | | 36/216 (16.7%) | 180/216 (83.3%) | | 6/217 (2.8%) | 211/217 (97.2%) | | 78/217 (35.9%) | 139/217 (64.1%) | | 104/216 (48.1%) | 112/216 (51.9%) | |
| Tight | 53/202 (26.2%) | 149/202 (73.8%) | | 41/202 (20.2%) | 161/202 (79.8%) | | 3/202 (1.5%) | 199/202 (98.5%) | | 51/202 (25.2%) | 151/202 (74.8%) | | 95/202 (47.0%) | 107/202 (53.0%) | |
| GDM at enrollment | | | 0.48 | | | 0.69 | | | - | | | 0.39 | | | 0.07 |
| Yes | | | | | | | | | | | | | | | |
| Less-tight | 11/32 (34.4%) | 21/32 (65.6%) | | 4/32 (12.5%) | 28/32 (87.5%) | | 0 | 32/32 (100%) | | 9/32 (28.1%) | 23/32 (71.9%) | | 18/31 (58.1%) | 13/31 (41.9%) | |
| Tight | 8/31 (25.8%) | 23/31 (74.2%) | | 6/31 (19.4%) | 25/31 (80.6%) | | 0 | 31 (100%) | | 8/31 (25.8%) | 23/31 (74.2%) | | 10/31 (32.3%) | 21/31 (67.7%) | |

| Prognostic factor and type of DBP control | Primary perinatal outcome (N=981 babies) | | p | SGA <10 th centile (N=976 babies) | | p | Secondary maternal outcome (N=981 women) | | p | Severe hypertension after randomization (N=981 women) | | p | Preeclampsia (N=979 women) | | p |
|---|--|--------------------|-------------|--|--------------------|-------------|--|--------------------|-------------|---|--------------------|-------------|---|--------------------|-----------------|
| | Yes | No | | Yes | No | | Yes | No | | Yes | No | | Yes | No | |
| | (155/493 in less-tight vs. 150/488 in tight) | | | (79/490 in less-tight vs. 96/486 in tight) | | | (18/493 in less-tight vs. 10/488 in tight) | | | (200/493 in less-tight vs. 134/488 in tight) | | | (241/ 491 in less-tight vs. 223/488 in tight) | | |
| | Yes N=305 | No N=676 | | Yes N=175 | No N=801 | | Yes N=28 | No N=953 | | Yes N=334 | No N=647 | | Yes N=464 | No N=515 | |
| No | | | | | | | | | | | | | | | |
| Less-tight | 144/461 (31.2%) | 317/461 (68.8%) | | 75/458 (16.4%) | 383/458 (83.6%) | | 18/461 (3.9%) | 443/461 (96.1%) | | 191/461 (41.4%) | 270/461 (58.6%) | | 223/460 (48.5%) | 237/460 (51.5%) | |
| Tight | 142/457 (31.1%) | 315/457 (68.9%) | | 90/455 (19.8%) | 365/455 (80.2%) | | 10/457 (2.2%) | 447/457 (97.8%) | | 126/457 (27.6%) | 331/457 (72.4%) | | 213/457 (46.6%) | 244/457 (53.4%) | |
| PMR of recruiting country | | | 0.78 | | | 0.34 | | | 0.17 | | | 0.42 | | | <0.01 |
| High (≥10/1000 births) | | | | | | | | | | | | | | | |
| Less-tight | 23/80 (28.8%) | 57/80 (71.3%) | | 11/80 (13.8%) | 69/80 (86.3%) | | 3/80 (4.8%) | 77/80 (96.3%) | | 27/80 (33.8%) | 53/80 (66.3%) | | 27/80 (33.8%) | 53/80 (66.3%) | |

| Prognostic factor and type of DBP control | Primary perinatal outcome (N=981 babies) | | p | SGA <10 th centile (N=976 babies) | | p | Secondary maternal outcome (N=981 women) | | p | Severe hypertension after randomization (N=981 women) | | p | Preeclampsia (N=979 women) | | p |
|---|--|--------------------|---|--|--------------------|---|--|--------------------|---|---|--------------------|---|---|--------------------|---|
| | Yes | No | | Yes | No | | Yes | No | | Yes | No | | Yes | No | |
| | (155/493 in less-tight vs. 150/488 in tight) | | | (79/490 in less-tight vs. 96/486 in tight) | | | (18/493 in less-tight vs. 10/488 in tight) | | | (200/493 in less-tight vs. 134/488 in tight) | | | (241/ 491 in less-tight vs. 223/488 in tight) | | |
| | N=305 | N=676 | | N=175 | N=801 | | N=28 | N=953 | | N=334 | N=647 | | N=464 | N=515 | |
| Tight | 21/80 (26.3) | 59/80 (74.8%) | | 18/79 (22.8%) | 61/79 (77.2%) | | 0/80 (0%) | 80/80 (100%) | | 14/80 (17.5%) | 66/80 (82.5%) | | 40/80 (50.0%) | 40/80 (50.0%) | |
| Low (<10/1000 births) | | | | | | | | | | | | | | | |
| Less-tight | 132/413 (32.0%) | 281/413 (68.0%) | | 68/410 (16.6%) | 342/410 (83.4%) | | 15/413 (3.6%) | 398/413 (96.4%) | | 173/413 (41.9%) | 240/413 (58.1%) | | 214/411 (52.1%) | 197/411 (47.9%) | |
| Tight | 129/408 (31.6%) | 279/408 (68.4%) | | 78/407 (19.2%) | 329/407 (80.8%) | | 10/408 (2.5%) | 398/408 (97.6%) | | 120/408 (29.4%) | 288/408 (70.6%) | | 183/408 (44.9%) | 225/408 (55.2%) | |

PMR (perinatal mortality ratio); SGA (small for gestational age)