Hypertensive disorders of pregnancy (HDP) complicate 5% to 10% of pregnancies and are increasing with the rising prevalence of cardiometabolic diseases in younger women. Normal pregnancy is marked by an initial drop in mean arterial pressure, with an eventual rise in blood pressure (BP) to prepregnancy levels. The development of HDP involves a number of factors that result in volume and hemodynamic alterations that fail to adapt to the changes accompanying pregnancy. There are well established associations between HDP and the development of maternal cardiovascular disease (CVD) later in life. Although the associations between preeclampsia and future CVD have long been known, newer evidence suggests that there are also long-term CVD risks associated with gestational hypertension (GH), although the etiology of GH is thought to be distinct from that of preeclampsia. Whether preeclampsia and GH result as manifestations of already preexisting CVD risk or whether they contribute to the pathogenesis of later CVD development is unclear. A history of HDP has the unique potential to identify women at higher risk of future CVD, for whom targeted risk-reduction interventions may be particularly helpful. In this review, we discuss the evidence for the long- and short-term risks of maternal CVD associated with HDP, with a focus on preeclampsia and GH. We also outline current recommendations for screening and prevention of CVD in women with a history of HDP and highlight important areas in which additional research is needed.

Classification and Epidemiology of HDP

The American College of Obstetricians and Gynecologists (ACOG) identifies 4 categories of HDP (Table 1). In this review, we focus on GH and preeclampsia within the term HDP. Of note, in 2017, the American College of Cardiology and American Heart Association (ACC/AHA) issued a clinical practice guideline on hypertension that reclassified the previous category of prehypertension into elevated BP (systolic BP 120–129 mm Hg) and stage 1 hypertension (systolic BP 130–139 mm Hg or diastolic BP 80–89 mm Hg). The ACOG guidelines do not incorporate the most recent hypertension definitions, and this is an area in which new evidence is essential. A recent reexamination of the high-risk aspirin trial data during pregnancy reported that the newly identified stage 1 hypertension in pregnancy was associated with increased risk of preeclampsia compared with normotensive women (39% versus 15%) and that randomization to aspirin reduced this risk (24% versus 39%).

Pathophysiology and Risk Factors

Uteroplacental insufficiency and a susceptible maternal vascular and metabolic phenotype converge as the underlying etiology of preeclampsia. It is well established, however, that the condition is heterogeneous, with multiple pathways leading to vasoconstriction and end-organ ischemia. Preeclampsia aggregates in families, and new evidence suggests that fetal genetic variants near FLT1 (fms-related tyrosine kinase 1), a gene involved in angiogenesis, may contribute to risk. Precise causes of preeclampsia are still unknown, but contributors are impaired angiogenesis, systemic endothelial dysfunction, and decreased vascular compliance resulting in impaired accommodation of the volume expansion required for healthy gestation. Importantly, preeclampsia involves multisystem dysfunction. There is evidence of structural and functional cardiac impairments in women during pregnancies complicated by preeclampsia. Biomarkers of cardiac remodeling are also elevated during these pregnancies.
It is unclear if GH has a distinct etiology from preeclampsia or perhaps is an early stage of a shared phenomenon. GH and preeclampsia have similar risk factors, such as obesity, parity, and history of prior preeclamptic pregnancies. There are race disparities in the risk factors and prevalence of both GH and preeclampsia, with black women carrying a higher burden of disease.\(^\text{16}\) Notably, the risk of adverse newborn outcomes is higher with preeclampsia than with GH. The risk of preterm delivery, for example, was found in one study to be 7.2\% in normotensive women, 12.5\% in women with GH, and 39.2\% in those with preeclampsia.\(^\text{17}\) Evidence also shows that the inflammatory signature may be distinct in women with GH compared with preeclampsia, with the possibility that women with GH can compensate more successfully.\(^\text{18}\) In contrast, preeclampsia is more often associated with placental disease characterized by impaired markers of angiogenesis.\(^\text{19}\) Progression to chronic hypertension postpartum may help further elucidate whether GH and preeclampsia have distinct etiologies. Specifically, 42\% of women with preeclampsia and 39\% of women with GH progress to hypertension after mean follow-up of 2.5 years compared with rates as low as 1\% among women with normotensive pregnancies.\(^\text{20,21}\)

The pathophysiologic mechanisms linking preeclampsia and GH to maternal CVD later in life are not well understood; however, several hypotheses have been proposed. A possibility is that HDP and subsequent CVD share common predisposing risk factors and are both manifestations of the same pathophysiologic processes at different times in a woman’s life. This possibility is supported by large cohort studies that have demonstrated strong associations between HDP and a number of typical CVD risk factors, including chronic hypertension, type 2 diabetes mellitus (DM), hyperlipidemia, and increased body mass index (BMI).\(^\text{22,23}\) Moreover, a prospective Norwegian study found that prepregnancy risk factors accounted for >50\% of the association between HDP and later life BP, BMI, and lipid levels.\(^\text{24}\) In addition, vascular insufficiency is commonly detected in the placentas of women with preeclampsia, and some of these lesions are characterized by inflammation and lipid-laden macrophages that are remarkably similar to features of early stage atherosclerotic plaques.\(^\text{25}\) These placental lesions may be an early expression of susceptibility to vascular impairments later in life.\(^\text{26}\) Another possible pathophysiologic mechanism is that future CVD is a direct result of endothelial dysfunction generated by HDP that persists after delivery. Several studies have demonstrated elevated markers of endothelial dysfunction,\(^\text{27–29}\) arterial stiffness,\(^\text{30,31}\) and systemic inflammation\(^\text{29,32}\) up to 8 years after pregnancies complicated by preeclampsia. Furthermore, preeclamptic women develop activating angiotensin II type 1 autoantibodies during pregnancy that persist after 18 months postpartum.\(^\text{33}\) Binding of these antibodies to the angiotensin 1 receptor has been shown to induce endothelial damage and may be a mechanistic link between preeclampsia and subsequent CVD risk.\(^\text{34}\) However, the relationship between preeclampsia and endothelial dysfunction is controversial, as other studies have failed to find an association between preeclampsia and functional markers of endothelial dysfunction, such as flow-mediated dilation.\(^\text{35,36}\) Moreover, these studies are small and limited in duration of follow-up. Further research to identify mechanisms linking preeclampsia and other HDP to future CVD is needed.

### HDP and Long-Term Risk of Maternal CVD

Numerous studies have established HDP as important risk factors for long-term maternal CVD and cardiovascular mortality (Figure).\(^\text{37–39}\) Of the HDP categories, the association between preeclampsia and future CVD risk has been studied most extensively. Several large meta-analyses, each studying >2 million women, found the risk of CVD to be roughly 2 times higher among women with a history of preeclampsia than women with normotensive pregnancies.\(^\text{40–42}\) More specifically, one meta-analysis demonstrated a 4.2-fold increased risk of heart failure, a 2.5-fold increased risk of coronary artery disease, and a 1.8-fold increased risk of stroke in women with preeclamptic pregnancies over a follow-

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**Table 1. ACOG Classification of Hypertension in Pregnancy\(^\text{3}\)**

| Condition                  | Definition                                                                 | Prevalence, % |
|----------------------------|---------------------------------------------------------------------------|---------------|
| GH                         | De novo BP elevations (>140/90 mm Hg) after 20 wks of gestation without   | 6–7           |
|                            | other organ system dysfunction                                             |               |
| Preeclampsia               | De novo BP elevations after 20 wks of gestation coupled with proteinuria or| 5–7           |
|                            | other end-organ dysfunction                                                |               |
| Chronic hypertension       | Elevated BP before 20 wks of gestation or persisting beyond 12 wks postpartum | 1–5           |
| Chronic hypertension with  | Increased BP and new-onset proteinuria or other end-organ dysfunction in addition | 0.2–1         |
| superimposed preeclampsia  | to preexisting hypertension                                                |               |

ACOG indicates American College of Obstetricians and Gynecologists; BP, blood pressure; GH, gestational hypertension.
up period of up to 39 years. The risk of future hypertension is even more pronounced, with increased risk ranging from 2.3- to 6.7-fold among women with prior preeclampsia. These women also have roughly double the risk of venous thromboembolism and 4 times the risk of DM compared with those with normotensive pregnancies. In addition, although preeclampsia is associated with only a modest increase in overall mortality, it has been found to be associated with a 1.7- to 3.6-fold increase in CVD mortality across various studies.

Notably, a dose-response relationship has been observed between the severity of preeclampsia and the long-term risk of CVD. In a meta-analysis of >2.3 million women, mild, moderate, and severe preeclampsia was associated with a relative risk of 2.00, 2.99, and 5.36, respectively, of developing future CVD. In another study analyzing specific cardiovascular outcomes, including hypertension, coronary artery disease, heart failure, stroke, venous thromboembolism, and DM, the risks of all above end points were increased in women with a history of severe preeclampsia.

### Figure
Associations among prepregnancy risk factors, hypertensive disorders of pregnancy, and postpregnancy risk of cardiovascular disease. Prepregnancy hypertension increases the risk of preeclampsia. Prepregnancy overweight status or obesity and diabetes mellitus increase the risk of development of gestational hypertension. The combination of small-for-gestational-age or preterm delivery with hypertensive disorders of pregnancy further increases the risk of future cardiovascular outcomes. +Mildly increased risk (hazard ratio <2 in most studies). ++Moderately increased risk (hazard ratio >2 in most studies). +++Markedly increased risk (hazard ratio >3 in most studies). CVD indicates cardiovascular disease; CVD, cardiovascular disease; HF, heart failure; HTN, hypertension.

|                | CVD | HTN | CAD | Stroke | HF | Mortality |
|----------------|-----|-----|-----|--------|----|-----------|
| Prepregnancy   |     |     |     |        |    |           |
| Overweight/Obesity | ++  | +   | +++ | ++     | +  | +         |
| Diabetes mellitus | ++  | ++  | +++ | ++     | +  | +         |
| Hypertension   |     | +++ | +++ | +++    | +++| +         |
| Pregnancy      |     |     |     |        |    |           |
| Gestational hypertension |     |     |     |        |    |           |
| Preeclampsia   |     |     |     |        |    |           |
| + Small for gestational age |     |     |     |        |    |           |
| + Preterm delivery |     |     |     |        |    |           |
| Postpregnancy  |     |     |     |        |    |           |
| CVD            | +++ | +++ | ++  | ++     | +  | +         |
| HTN            | ++  | +++ | +++ | ++     | +  | +         |
| CAD            | +++ | +++ | +++ | ++     | +  | +         |
| Stroke         | +   | +++ | ++  | ++     | +  | +         |
| HF             | +   | +++ | +++ | ++     | +  | +         |
| Mortality      | +   | +++ | +++ | +++    | +++| +         |

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compared with those with mild preeclampsia. The same authors found in another study that women with severe preeclampsia have a 2.9-fold greater risk of future death from cardiovascular causes than women with normotensive pregnancies, compared with a 2-fold greater risk in women with mild preeclampsia.

In addition to the severity of preeclampsia, recurrent preeclampsia and preeclampsia superimposed on chronic hypertension are also associated with additional increases in CVD risk. Women with recurrent preeclampsia have a higher incidence of cardiovascular hospitalization (281.4 versus 167.7 per 1000 women) and a shorter time to first cardiovascular event (12.7 versus 11.6 years) compared with women who experienced preeclampsia in only 1 pregnancy.

Chronic hypertension with superimposed preeclampsia or eclampsia has been shown to be associated with a greater risk of future CVD (hazard ratio [HR]: 2.06; 95% confidence interval [CI], 1.61–2.65) than either chronic hypertension (HR: 1.66; 95% CI, 1.46–1.88) or preeclampsia (HR: 1.40; 95% CI, 1.11–1.76) alone.

Compared with preeclampsia, the relationship between GH and subsequent maternal CVD risk has been studied to a lesser extent. Just as a racial disparity exists in the prevalence of GH, the association between GH and maternal CVD risk may also differ by race. A study of the Child Health and Developmental Studies cohort found that black women with a history of GH had an 80% increased CVD mortality compared with those without pregnancy complications, whereas non-black women with GH did not experience increased CVD mortality. However, other studies in largely white populations have demonstrated increased CVD mortality with GH.

The risk of future CVD with GH has generally been found to be lower than that associated with preeclampsia, however, some recent studies have actually identified a higher risk of CVD associated with GH. A study of a Finnish cohort with 39 years of follow-up found that GH was associated with modestly higher CVD risk than preeclampsia (HR: 1.45 versus 1.40). Of note, the risk of future coronary artery disease, heart failure, hypertension, cerebrovascular disease, DM, and chronic kidney disease in this study were all found to be higher with GH than with preeclampsia in this study. Similar findings were demonstrated in a study of >31 000 women followed over a median of 20 years, in whom the risk of future hypertension (odds ratio: 4.08 versus 3.06) and ischemic heart disease (odds ratio: 3.19 versus 2.67) was found to be higher with GH than with preeclampsia.

Given the growing evidence that GH may be just as important a contributor to CVD risk as preeclampsia, the long-term CVD morbidity associated with GH warrants further study. In an article published recently, Riise et al explored the associations between GH and CVD, as well as the additional contributions of other adverse pregnancy outcomes, in a large cohort of >600 000 women. The authors found that GH in the first pregnancy was associated with an 80% higher risk of subsequent CVD. This risk was amplified in women who experienced GH in their second pregnancy compared with the first. Of note, the risk of maternal CVD with GH was similar to that of preeclampsia. This study further emphasizes the importance of GH as a strong predictor of future CVD risk. Its exploration of the risk associated with GH in combination with other adverse pregnancy outcomes has important implications for identification of high-risk women for targeted prevention efforts.

An aspect of CVD risk that has not been previously examined is the relationship between HDP and atrial fibrillation, which is explored by Scantlebury et al in a recent issue of the Journal of the American Heart Association (JAHA). In a nested case–control study conducted within a cohort of >7000 women, 105 cases of atrial fibrillation were compared with 105 controls. Women with atrial fibrillation were 2.6 times more likely to have had a history of HDP. This association appeared partially mediated by obesity during pregnancy and postpartum hypertension, as it was attenuated and no longer statistically significant after adjusting for these factors. This study adds to the current literature on the link between HDP and future structural heart disease and provides evidence for increased screening of CVD after pregnancies complicated by HDP. It also highlights the importance of progression to chronic hypertension in these pathways linking HDP to CVD.

Importantly, existing studies to date have yet to analyze the associations between stage 1 hypertension, as defined by the 2017 ACC/AHA hypertension guidelines, and future maternal CVD risk. It has been shown, however, that isolated systolic and diastolic hypertension during pregnancy are associated with increased risk of subsequent hypertension and CVD. Another study reported that modestly elevated BP during pregnancy (>120/80 mm Hg without HDP) was associated with a 2.6-fold higher risk of chronic hypertension in the decade after delivery compared with women with lower BP. Given the evidence that accumulation of exposure to even modest BP elevations across adulthood increases CVD risk, further investigation into the long-term implications of modest BP elevation during pregnancy is crucial.

HDP and Early to Midterm Risk of Maternal CVD

Understanding the early (within the first year) and midterm (up to 10 years) risk of CVD after pregnancies complicated by HDP may provide insight into the progression to long-term cardiovascular consequences and optimal timing of postpartum prevention strategies. In addition, the presence of early CVD events has implications on maternal morbidity during
future pregnancies and long-term CVD risk thereafter. Unfortunately, the majority of studies on the association between HDP and CVD focus on long-term CVD risk, and limited data are available to address early and midterm risk. A retrospective cohort study of >300 000 women found that preeclampsia was associated with a 42% greater risk of CVD within the first 5 years postpartum, even after adjusting for demographic, socioeconomic, and other CVD risk factors.56 GH was associated with an 18% increase in 5-year CVD risk; however, the significance was attenuated after adjustment. In addition, women with HDP have been found to have a roughly 2.4-fold greater adjusted odds of hospitalization due to cardiovascular causes within 3 years of delivery compared with those without HDP.57 Another study examining hospitalizations due to CVD events showed that women with GH, mild preeclampsia, and severe preeclampsia had 2.8-fold, 2.2-fold, and 3.3-fold increased risk of CVD events, respectively, over a mean follow-up of 7.8 years.45

The recently published article by Egeland et al in JAH\A attempts to extend and update currently available data pertaining to early and midterm risk in women with pregnancy complications, focusing on inclusion of important CVD risk factor covariates in their analyses.58 The authors found that preeclampsia and GH were associated with 6- and 7-fold increased risk of pharmacologically treated hypertension, respectively, within 10 years of delivery. To specifically assess the early impact of preeclampsia and GH on the risk of hypertension, the authors analyzed hypertension risk at varying lengths of follow-up. The risk of hypertension after the combined exposure of preeclampsia and GH was greatest after 4 years (HR: 9.4; 95% CI, 8.0–11.0) and declined with increasing follow-up time. A similar result was reported by Behrens et al, who found that in the year after delivery, women with HDP had 12- to 25-fold higher rates of hypertension than did women with normotensive pregnancies.59 The rates remained 3- to 10-fold higher from 1 to 10 years postpartum and decreased to roughly twice as high at ≥20 years postpartum. These results and work from other studies demonstrate that preeclampsia and GH have a significant impact on CVD risk and risk factors as soon as a few years after delivery and even within the first year, which has important implications for the timing of preventive interventions. Discovery of markers identifying women at the highest risk of developing hypertension or other CVD risk factors would be helpful in developing an algorithm to assess and initiate prevention measures. A study of 600 Korean women with HDP, of whom 41 had persistent hypertension after 6 months postpartum, identified early onset hypertension with end-organ dysfunction, prepregnancy BMI, and history of smoking as independent risk factors for progression to chronic hypertension.60 In a study of >54 000 women participating in the Nurses’ Health Study II, obesity was found to increase the risk for chronic hypertension regardless of history of HDP.51 However, having higher BMI conferred an excess risk for chronic hypertension among women with HDP. This was not seen with other lifestyle risk factors such as physical activity, the DASH (Dietary Approaches to Stop Hypertension) diet, or sodium/potassium intake. These findings suggest that maintaining normal BMI may be particularly important in reducing a woman’s risk of chronic hypertension if she has a history of HDP. More research in this field is warranted to further explore these associations.

Additional Impact of Other Pregnancy-Related Complications on Maternal CVD Risk

Although this review is focused on HDP, it is important to note that other pregnancy-related complications, including delivery of a small-for-gestational-age infant and preterm delivery, further increase maternal CVD risk when occurring in combination with HDP (Figure).52–65 In a recent JAH\A article by Riise et al, the HR for risk of CVD associated with GH plus small-for-gestational-age and/or preterm delivery was 2.6, compared with 1.8 for GH alone, 1.1 for small for gestational age alone, and 1.3 for preterm delivery alone.52 In terms of midterm risk, the study by Egeland et al in a recent issue of JAH\A demonstrated that over median follow-up of 7.1 years, the combination of preeclampsia and GH with a very preterm delivery (<32 weeks gestation) was associated with a markedly elevated risk of CVD that is 12.7-fold higher than normotensive term pregnancies.58 A history of preeclampsia and GH plus delivery of a very small-for-gestational-age infant (<2.5%) was associated with a 5.3-fold increased risk of CVD.

Current Guidelines and Recommendations

Given that HDP has significant implications for future maternal CVD risk, the questions of when to treat HDP and how to identify high-risk women for preventive intervention are important to answer. Multiple guidelines on the management of hypertension in pregnancy exist; however, no clear consensus currently exists on the optimal BP threshold at which to initiate antihypertensive treatment and the target BP to achieve (Table 2). In addition, there is little guidance on how to interpret the 2017 ACC/AHA clinical guidelines on hypertension as they apply to pregnancy. The 2017 ACC/AHA guidelines stemmed from recent clinical trials that have demonstrated that achieving intensive BP reduction (systolic BP <120 mm Hg) resulted in a significant decrease in the risk of CVD events and mortality compared with BP reduction to within the range currently termed stage 1 hypertension (systolic BP 130–139 mm Hg or diastolic BP 80–89 mm Hg).66–68 The threshold for BP
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The long-term risk of maternal CVD with lower BP treatment thresholds and treatment targets during pregnancy is currently unclear, and additional work to understand this topic is crucial.

Pregnancy occurs relatively early in a woman’s lifespan, often before the onset of clinical CVD; therefore, the presence of HDP can uniquely serve as an early indicator of future CVD risk and can offer an opportunity to initiate meaningful risk-reduction strategies. Among women with preeclampsia, common cardiometabolic risk factors, such as elevated BP, cholesterol, and HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) scores, become evident as early as within the first year postpartum. This suggests that early screening and intervention for these modifiable risk factors may be an effective prevention strategy, although this has never been directly tested. Unfortunately, evidence indicates that there is limited physician awareness of the future CVD risks associated with HDP and of the benefits of screening. In 2011, the ACC/AHA published updated guidelines for the prevention of CVD in women that now include pregnancy history, including GH and preeclampsia, in the CVD risk assessment algorithm. The European Society of Cardiology and the National Institute for Health and Care Excellence also have guidelines for the management of arterial hypertension that directly tested. Unfortunately, evidence indicates that there is limited physician awareness of the future CVD risks associated with HDP and of the benefits of screening.72,73 The European Society of Cardiology and the National Institute for Health and Care Excellence also have guidelines for the prevention of CVD in women that now include pregnancy history, including GH and preeclampsia, in the CVD risk assessment algorithm.74 The European Society of Cardiology and the National Institute for Health and Care Excellence also have guidelines for the management of arterial hypertension that discuss the need to recognize long-term cardiovascular consequences of HDP.75,76

Various society guidelines have made recommendations regarding the initiation of prevention efforts (Table 2); however, these recommendations lack specificity, and there is no consensus on the when to initiate postpartum screening and the frequency and duration of monitoring. In line with this, ACOG and the AHA recently released a Presidential Advisory emphasizing the critical importance of a partnership among obstetricians and gynecologists, cardiologists, and primary care physicians to optimize early identification and modification of risk factors for heart disease in women.77

Additional areas where further research is needed include data on the implementation of risk stratification tools and...
calculators incorporating pregnancy history and specific pregnancy complications. Furthermore, there is a dearth of evidence regarding the long-term effectiveness of specific risk-reduction interventions. A small study of lifestyle interventions implemented at a hospital-based postpartum preeclampsia clinic found a significant improvement in physical activity and a nonsignificant improvement in weight 4.4 months after delivery. Future studies on the effectiveness of such interventions with longer term follow-up are essential.

Conclusions
HDP, including preeclampsia, GH, chronic hypertension, and superimposed preeclampsia, has been shown in a multitude of large, epidemiological studies to be associated with future maternal CVD risk and mortality. This relationship exists for both long-term CVD risk and CVD that develops within the first 10 years postpartum. Despite limited studies evaluating the early and midterm risk of CVD after HDP, studying this risk is important to understand the development and progression of future maternal CVD. Given the substantial evidence that HDP is associated with significantly increased risk of CVD, the ACC/AHA guidelines now include pregnancy complications as a major CVD risk factor. Additional research is needed to elucidate the appropriate BP targets in pregnancy, the optimal utilization of pregnancy complication history in risk stratification tools, and the effectiveness of preventive interventions.

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