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REVIEW ARTICLE

# Hypertensive pregnancy disorder, an under-recognized women specific risk factor for heart failure?

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During pregnancy, the maternal cardiovascular (CV) system undergoes major haemodynamic alterations ensuring adequate placental perfusion and a healthy pregnancy course. Hypertensive disorders of pregnancy (HDP) occur in almost 10% of gestations and preeclampsia, a more severe form, in 3–4%. Women with HDP demonstrated impaired myocardial function, biventricular chamber dysfunction and adverse biventricular remodelling. Shortly after delivery, women who experienced HDP express increased risk of classic CV risk factors such as hypertension, renal disease, abnormal lipid profile, and diabetes. Within the first two decades following a HDP, women experience increased rates of heart failure, chronic hypertension, ischaemic heart and cerebral disease. The mechanism underlying the relationship between HDP in younger women and CV disease later in life could be explained by sharing pre-pregnancy CV risk factors or due to a direct impact of HDP on the maternal CV system conferring a state of increased susceptibility to future metabolic or haemodynamic insults. Racial disparities in CV risk and social determinants of health also play an important role in their remote CV risk. Although there is general agreement that women who suffered from HDP should undertake early CV screening to allow appropriate prevention and timely treatment, a screening and intervention protocol has not been standardized due to limited available evidence. In this review, we discuss why women with hypertensive pregnancy may be disproportionately affected by heart failure with preserved ejection fraction and how cardiac remodelling during or after pregnancy may influence its development.

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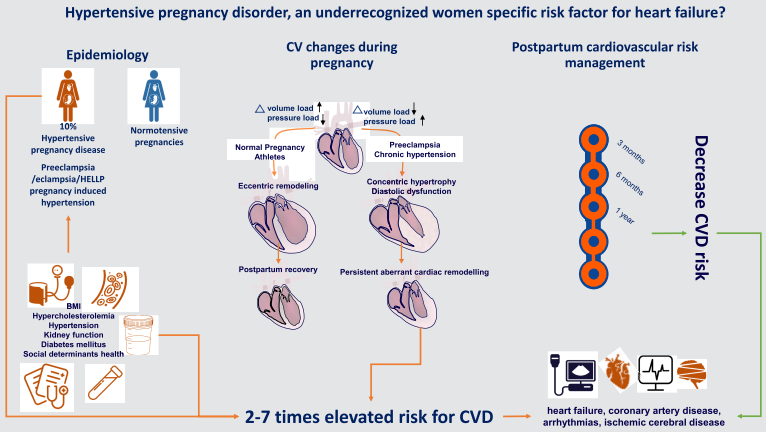
## Graphical Abstract




Hypertensive disorders of pregnancy as a risk factor for heart failure. BMI, body mass index; CV, cardiovascular; CVD, cardiovascular disease; HELLP, haemolysis, elevated liver enzymes, low platelet count.

**Keywords** Pregnancy • Hypertensive pregnancy disorders • Preeclampsia • Cardiovascular disease in women • Prevention

# Introduction

## Haemodynamic changes in normotensive pregnancy

During pregnancy, the maternal cardiovascular (CV) system undergoes major haemodynamic alterations ensuring adequate placental perfusion and a healthy pregnancy course.[1,2] Pregnancy-induced decrease in peripheral vascular resistance together with increased plasma volume promote reversible eccentric hypertrophy resembling the cardiac remodelling seen in endurance athletes (*Figure 1*)[3].

## Hypertensive disorders of pregnancy

Hypertensive disorders of pregnancy (HDP) including pregnancy-induced hypertension, preeclampsia and HELLP syndrome (haemolysis, elevated liver enzymes, low platelet count), occur in almost 10% of gestations and are a major cause of maternal death.[4] Preeclampsia, a multi-organ pregnancy disorder characterized by endothelial dysfunction, hypertension and multi-organ hypoperfusion, occurs in 3–4% of gestations in the Western world.[5] Any HDP is a marker of future CV disease (CVD) risk including cerebral vascular accidents, cardiac atherosclerotic event, atrial fibrillation, heart failure and cardiac death with a dose effect risk resulting in the highest risk being present in early- and preterm- preeclampsia. Conventional risk factors for heart failure include hypertension, coronary artery disease (CAD), myocardial infarction, obesity, atrial fibrillation, and renal disease, all of which are highly present after HDP.[6–12] Worse profiles in CV risk continue as early as 1 year postpartum after preeclampsia including higher levels of blood pressure (BP), low-density lipoprotein cholesterol, markers of insulin resistance and body mass index (BMI).[13,14] Hypertension after preeclampsia explained 64% of the increased risk of CAD and 49% of the increased risk of heart failure in these women.[7,11]

## Screening

There is general agreement that women who suffered from HDP should undergo CV screening starting as early as possible to make women aware of their increased CV risk and allow appropriate prevention. Although the exact modality of screening and protocol of intervention has not been standardized, mainly due to limited available evidence-based clinical research on antenatal and postnatal care, recent evidence suggests a potential role for early BP control with angiotensin-converting enzyme inhibitors.[15] Whether this will result in improved reverse remodelling and prevention of heart failure is subject for future research. Established and cost-effective prevention strategies should be implemented in regular clinical care.

# Definition and classification of hypertensive disorders of pregnancy

During pregnancy, hypertension is defined as systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg. Severe hypertension

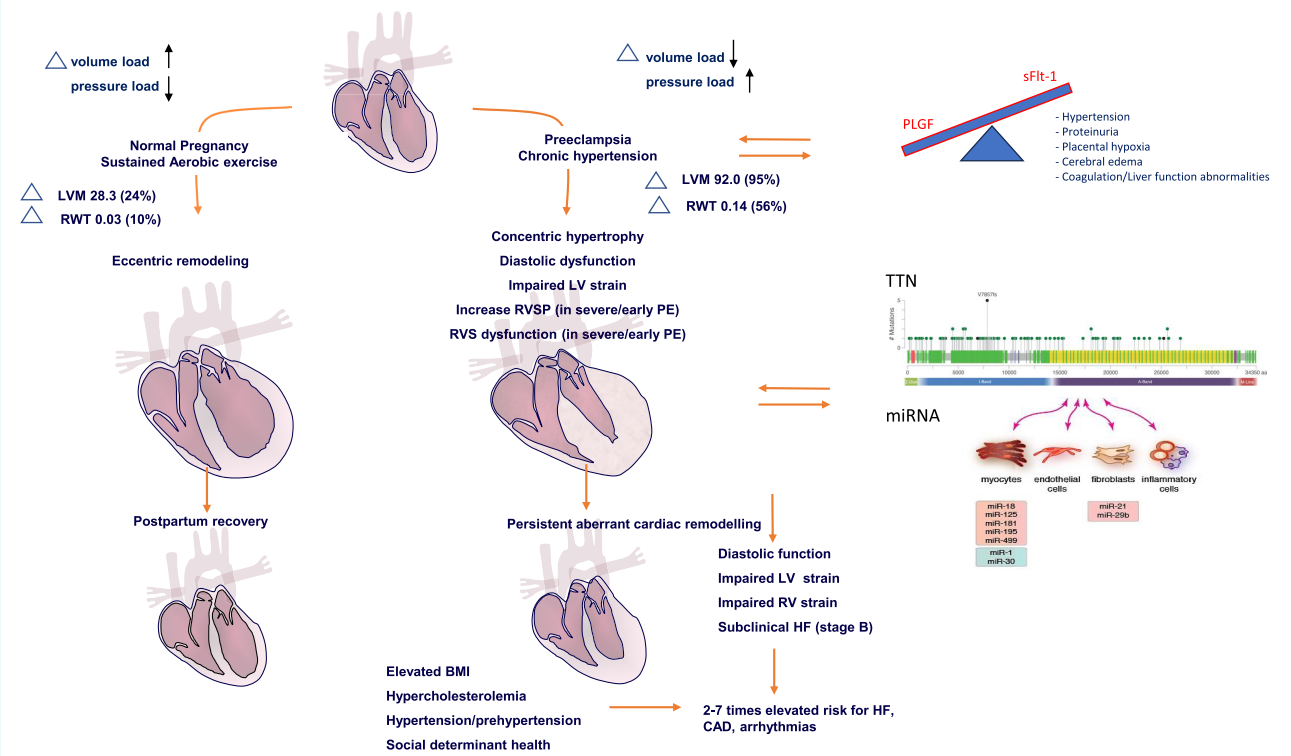



**Figure 1** In a normal pregnancy there is an increase in volume load and lower pressure load. The left ventricular mass (LVM) increases in these women with a minimum rise in relative wall thickness (RWT) resulting in eccentric hypertrophy. In a preeclamptic pregnancy, the change in volume load is shallow and pressure load increases significantly resulting in concentric remodelling, diastolic dysfunction, impaired left ventricular (LV) strain, increased right ventricular systolic pressure (RVSP) and right ventricular systolic (RVS) dysfunction (latest two mainly in severe/early preeclampsia). After preeclampsia, the prevalence of diastolic dysfunction, impaired LV and right ventricular (RV) strain and subclinical heart failure (HF stage B) remain high at a relative young age. These changes may not always be reversible and may persist or deteriorate, especially in persistent of metabolic, lifestyle or pressure factors and may contribute to the 2–7 times elevated risk for cardiovascular disease. The presenting symptoms and clinical signs of preeclampsia are thought to be triggered by abnormally high levels of soluble fms-like tyrosine kinase-1 (sFlt-1) and low placental growth factor (PlGF) – commonly referred to as 'angiogenic imbalance'. sFlt-1 is a protein that acts as an anti-angiogenic factor, meaning it interferes with the formation of new blood vessels. In preeclampsia, sFlt-1 levels become abnormally high, disrupting normal blood vessel function. PlGF is a protein that promotes the growth of blood vessels. In preeclampsia, PlGF levels are abnormally low, further worsening the blood vessel issues. Preeclampsia and cardiovascular disease also share several overlapping microRNA (miRNA) expression. Women who develop preeclampsia are more likely to carry protein-altering mutations in genes associated with cardiomyopathy, particularly in titin (TTN). Whether these mutations relate to the associated aberrant cardiac remodelling seen in preeclampsia is currently unknown. CAD, coronary artery disease. Adapted from Ghossein-Doha *et al.*[3]

is defined as systolic BP ≥160 mmHg and/or diastolic BP ≥110 mmHg.[16] The American College of Cardiology (ACC) and the American Heart Association (AHA) have endorsed a lower threshold for diagnosing hypertension in non-pregnant patients (systolic BP ≥130 mmHg or diastolic BP ≥80 mmHg). Some have suggested that this definition may also be appropriate for pregnant patients.[17] However, use of the lower threshold has not been widely studied, would increase the incidence of hypertension in pregnancy by about 10%, and could increase potentially unnecessary testing, hospitalization, and intervention in the absence of a proven benefit. The clinical importance of distinguishing preeclampsia from other HDP, namely, chronic and gestational hypertension, relates to its greater risk of adverse maternal and perinatal outcomes.[18]

## Traditional and revised definition of preeclampsia

The traditional definition of preeclampsia refers to the new onset of hypertension and proteinuria after 20 weeks of gestation or postpartum.[16,19–21] However, it is well recognized that many women with chronic or gestational hypertension still suffer from complications associated with preeclampsia such as pulmonary oedema, placental abruption, preterm delivery, perinatal death, small-for-gestational-age infants, and neonatal respiratory distress syndrome.[22–24]

To better reflect the risk of adverse pregnancy complications among women with a HDP, the definition of preeclampsia has been revised to include cases without proteinuria but with evidence

**Table 1 Subtypes of hypertensive pregnancy disorders**

| Subtype | Description |
|---|---|
| Gestational hypertension | Hypertension without proteinuria or other signs/symptoms of preeclampsia-related end-organ dysfunction that develops after 20 weeks of gestation in a patient with a previously normal blood pressure which resolves by 12 weeks postpartum |
| Early onset preeclampsia | Preeclampsia developing <34 weeks of gestation |
| Late onset preeclampsia | Preeclampsia developing ≥34 weeks of gestation |
| Preterm preeclampsia | Preeclampsia leading to delivery <37 weeks of gestation |
| HELLP syndrome | Haemolysis, elevated liver enzymes, low platelet count; a subtype of preeclampsia with severe features in which haemolysis, elevated liver enzymes, and thrombocytopenia are the predominant features |
| Severe preeclampsia | Patiënts who have severe hypertension and/or signs or symptoms of significant end-organ dysfunction that signify the severe end of the preeclampsia spectrum |
| Superimposed preeclampsia | When preeclampsia occurs in a patient with pre-existing chronic hypertension that precedes pregnancy or is present on at least two occasions before the 20th week of gestation or persists longer than 12 weeks postpartum |
| Eclampsia | Occurrence of a tonic–clonic seizure in a patient with preeclampsia in the absence of other neurologic conditions that could account for the seizure. |

of maternal end-organ or uteroplacental dysfunction. This 'broad' definition has now been adopted by most national and international clinical practice guidelines.[25–28] Several subtypes of preeclampsia exist (*Table 1*), with a variety of pathophysiological pathways leading to maternal and foetal mortality and morbidity.[29] The clinical features overlap, but the spectrum of disease and outcomes differ: early-onset disease has been associated with poorer severe placental and maternal/foetal outcomes.[30–32]

# Prevalence of hypertensive disorders of pregnancy

## Prevalence around the world

Hypertensive disorders of pregnancy are estimated to occur in 10% of pregnancies.[33–35] Precise estimate of HDP prevalence depends on the definition of HDP and the subtype. Most clinical practice guidelines use the ISSHP or ACOG definitions updated in 2018 and 2019, respectively. There is substantial regional variation with highest incidence in Sub-Saharan Africa and Southeast Asia and lowest in Australasia, Oceania, and Central Asia.[36] Based on the Global Burden of Disease Study, the worldwide incidence increased from 16.3 million to 18.08 million from 1990 to 2019.[36–38]

## Risk factors for increasing prevalence

Age-standardized incidence rates are higher in areas with lower sociodemographic or development indices, rural areas, and in lower and older age groups[36] (*Figure 2*). In the United States, rates of HDP in delivery hospitalizations almost doubled from 1990 to 2014.[35] Rising rates of HDP have been attributed to advanced maternal age and risk factors for CVD such as chronic hypertension, obesity, and diabetes. Chronic hypertension prevalence in pregnancy is estimated at 1–2% and has been rising over time.[35–37] A meta-analysis of 265 270 patients from Europe, North American and Oceania cohorts found increasing prevalence with increasing pre-pregnancy BMI and increasing gestational weight gain.[39] A separate analysis attributed almost a quarter of complications to overweight or obesity defined as a BMI >25 kg/m$^2$.[40]

# Cardiovascular origins of the pathophysiology of hypertensive disorders of pregnancy

Preeclampsia is a multi-organ pregnancy disorder which is characterized predominantly by CV manifestations of hypertension and multi-organ hypoperfusion.[5,41] The underlying biological mechanisms are not fully understood. Recent evidence suggests that preeclampsia is not merely a placental disorder. Suboptimal maternal CV performance resulting in secondary uteroplacental hypoperfusion may lead to the development of preeclampsia (*Figure 3*). It is no coincidence that most therapeutic prevention strategies for preeclampsia employ drugs used to reduce the incidence of CVD in non-pregnant adulthood, such as low-dose aspirin, calcium, metformin and antihypertensive medications.[42] These commonalities further strengthens the hypothesis of a CV origin for preeclampsia. The major established risk factors for preeclampsia are related to increased CV risk in later life. The commonality of these risk factors for preeclampsia with those for CVD support the hypothesis for a central role of impaired maternal CV function in determining poor placentation secondary to malperfusion.

## Cardiac adaptation during normotensive pregnancy

During normal pregnancy, there is a significant shift in maternal haemodynamics, with a decrease in peripheral vascular resistance, a consequent increase in renin–angiotensin–aldosterone system activity and a large increase in circulating plasma volume with an increase of cardiac output up to 50%.[2] The increased volume load and decreased pressure load, are accompanied by physiological

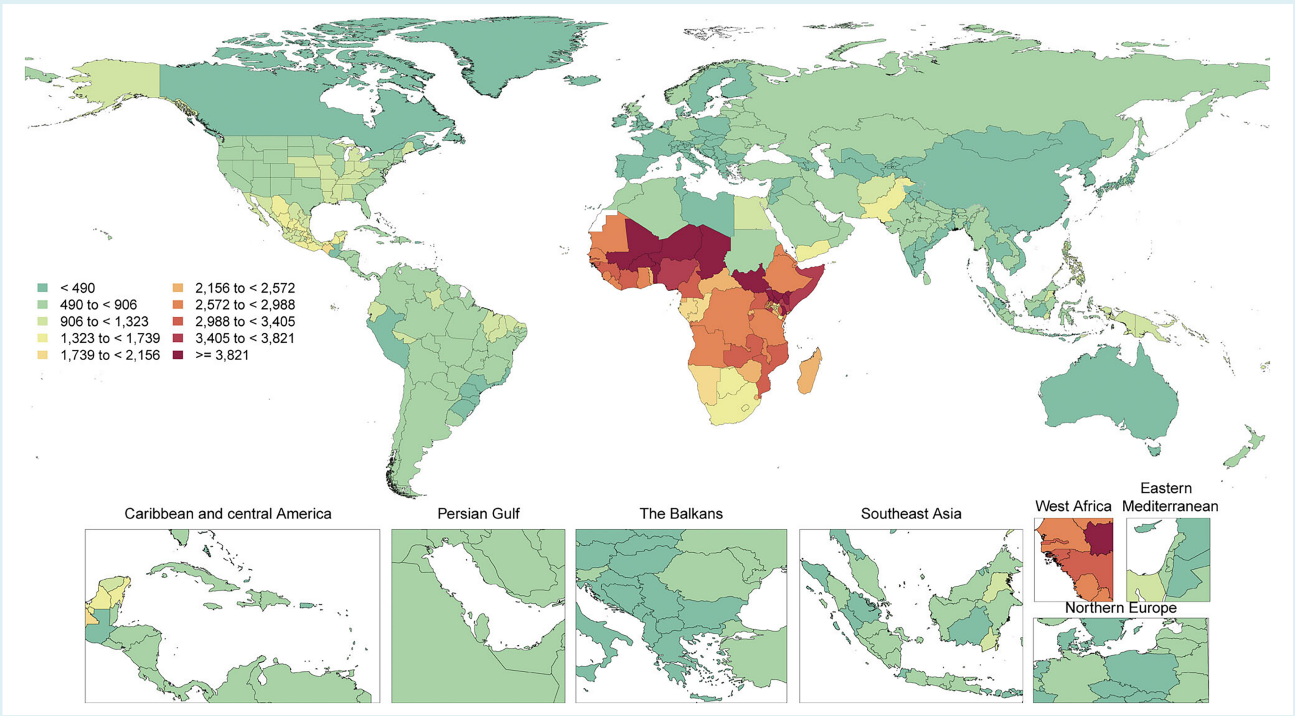



**Figure 2** Global incidence rates of maternal hypertensive disorders per 100 000 females, 15 to 49 years of age, 2021. (Data courtesy of the Global Burden of Disease Study. Institute for Health Metrics and Evaluation. All rights reserved).

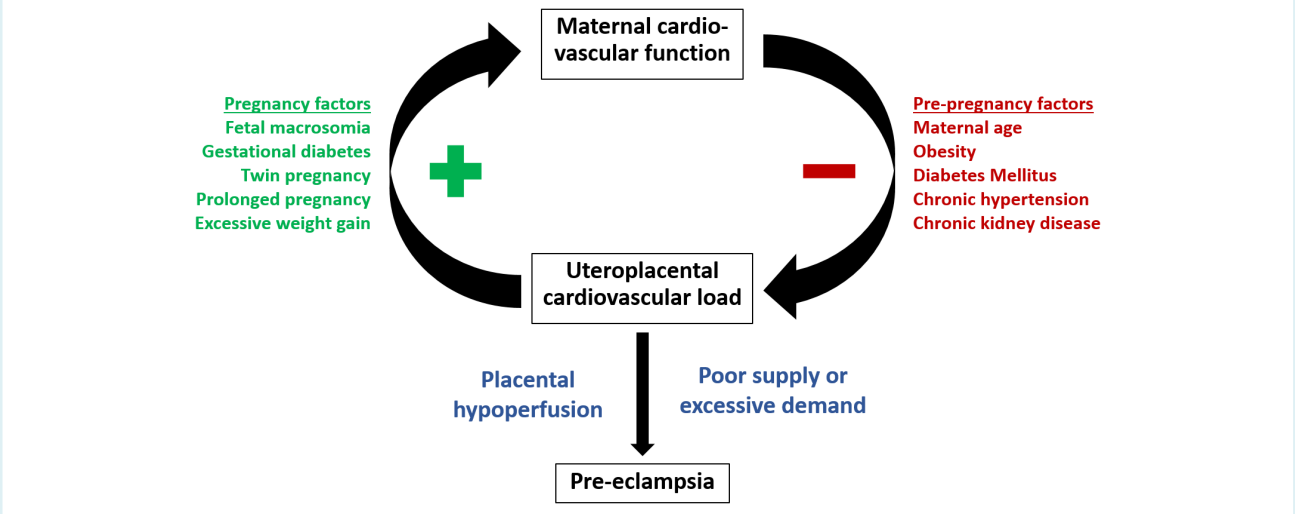



**Figure 3** Pathophysiology of preeclampsia. Placental hypoperfusion either due to asymptomatic cardiac dysfunction or excessive pregnancy demand may lead to preeclampsia following the same translational mechanisms previously described for the placental aetiology hypothesis.

cardiac adaptation resulting in increased left ventricular (LV) mass, increased LV end-diastolic diameter resulting in a slight increase in relative wall thickness and with eccentric remodelling. There is also increased LV wall thickness, increased left atrial size and a small reduction in LV diastolic function.[2] LV systolic function remains preserved. These changes are thought to resolve between 1 and 6 months following pregnancy, with CV adaptations returning to a pre-pregnancy state, in a process known as reverse remodelling.[43]

## Cardiac adaptation during hypertensive pregnancy

Numerous studies have demonstrated that women affected by preeclampsia present with a haemodynamic pattern of high total vascular resistance and low cardiac index.[1,44,45] In a preeclamptic pregnancy, the change in volume load is shallow and pressure load increases significantly resulting in concentric remodelling, diastolic

dysfunction, impaired LV strain, increased right ventricular systolic pressure (RVSP) and right ventricular systolic dysfunction (latest two mainly in severe/early preeclampsia).

Women destined to develop preeclampsia are known to have poorer pre-pregnancy haemodynamic indices compared to women destined to have an uneventful pregnancy.[46] The abnormalities are in some cases even found before preeclampsia is clinically evident.[47–50] Abnormalities in several cardiac parameters (LV remodelling, diastolic function, total vascular resistance, cardiac index, E/e' ratio and LV mass index) are evident at mid-gestation in women several weeks before they develop clinical signs and symptoms of preeclampsia.[47–50] These findings demonstrate that maternal CV maladaptation precedes the development of preeclampsia and may play a central role in the pathophysiology of this disease, probably through trophoblast malperfusion, impaired placentation and the subsequent development of preeclampsia. In support of this mechanism, the relationship between cardiac function before pregnancy and uteroplacental Doppler flow patterns during pregnancy has been confirmed in a recent meta-analysis.[51]

## Potential genetic and molecular mechanisms

Women who develop preeclampsia are more likely to carry protein-altering mutations in genes associated with cardiomyopathy, particularly in titin (TTN).[52] Whether these mutations relate to the associated aberrant cardiac remodelling seen in preeclampsia is currently unknown. Familial clustering has also been reported supporting a link to genetic causality. The limited number of genetic loci that have been consistently linked to preeclampsia, have also been implicated in adult CVD.[53] Preeclampsia and CVD also share several overlapping microRNA expression that relate to cardiomyocyte remodelling and fibrosis.[54] The presenting symptoms and clinical signs of preeclampsia are thought to be triggered by abnormally high levels of soluble fms-like tyrosine kinase-1 (sFlt-1) and low placental growth factor (PlGF). sFlt-1 is a protein that acts as an anti-angiogenic factor, meaning it interferes with the formation of new blood vessels. In preeclampsia, sFlt-1 levels become abnormally high, disrupting normal blood vessel function. PlGF is a protein that promotes the growth of blood vessels. In preeclampsia, PlGF levels are abnormally low, further worsening the blood vessel issues. This imbalance of high sFlt-1 and low PlGF is referred to as the 'angiogenic imbalance', and it plays a key role in the development of preeclampsia (*Figure 1*). Even though these angiogenic factors are known to be secreted into the maternal circulation from the placenta, they are also known to be deranged in non-pregnant individuals and children with various forms of CV dysfunction.

## Social determinants of health and cardiovascular disease

The development of chronic hypertension after pregnancies complicated by preeclampsia only partly explains the increased risk of subsequent CVD.[55] One of the largest knowledge gaps are how social determinants of health (SDOH)—resulting from environmental factors that affect how one lives, learns, and works—affects HDP and CVD.[56] Examples of SDOH include economic stability, access to health, education quality, social and neighbourhood environments. Originally, Black race was thought to be a large risk factor for preeclampsia and CVD—where racial disparities in health clearly exist. In the United States, Black women are 3.5 times more likely to succumb to maternal mortality compared to their White counterparts. When the cause of maternal mortality was further categorized, Black women were five times more likely to die from CV conditions in comparison to their white counterparts.[57] In a UK based cohort, women admitted with pregnancy-related heart failure with preserved ejection fraction (HFpEF) were more likely to be of Black ethnicity, as well as older, and poorer,[58] suggesting socioeconomic risk factors may play a role in addition to biological risk factors.

Although racial disparities exist, race is a social construct rather than a biological determinant. The content of melanin in one's skin or the language one speaks do not explain why these stark health disparities exist.[59] However, institutional racism invariably impacts on the health encounters of Black and Brown persons contributing to inequities in their maternal and CV outcome. For this reason, stratification and prevention algorithms will continue to underperform until SDOH are important variables and included in said algorithms.[60]

# Long-term maternal health after preeclampsia

## Increased general cardiovascular risk after hypertensive disorders of pregnancy

There is an abundance of evidence demonstrating increased CVD morbidity and mortality throughout the lifetime.[61,62] CVD mortality studies show that a history of preeclampsia increases risk of dying two- to five-fold from CVD regardless of follow-up time.[61,63–65] Women with preterm/early-onset preeclampsia have an even higher risk of developing congestive heart failure and CAD compared with women who suffered from term/late-onset preeclampsia.[61]

## Higher incidence of heart failure after hypertensive disorders of pregnancy

Multiple epidemiological studies now show that the incidence of heart failure is higher in women with previous HDP. A Norwegian registry study showed in 119 500 000 women lower rates of heart failure free survival over a 30-year period.[66] Williams *et al.*[67] studied hospitalizations for heart failure, in particular hospitalizations for HFpEF and found that readmissions with HFpEF were twice as likely in a group of women with previous hypertensive pregnancy, with median time of onset being only 32.2 months post-delivery. In line with these findings, women who had at least one pregnancy affected by preeclampsia had a hazard ratio of 2.13 for heart failure in a UK based study among 250 women with a follow-up time of 20 years.[65] In this cohort, 65% of all CV disorders had occurred in women aged below 40. Studies using imaging such as echocardiography to follow

up women post hypertensive pregnancy have also shown changes more consistent with HFpEF. Boardman *et al.*[68] showed that women 5–10 years post hypertensive pregnancy had increased LV mass, increased left atrial volume, and reduced functional capillary density, compared to women who had normotensive pregnancy.

### Persistent abnormal cardiac remodelling after delivery

The adverse cardiac morphological and functional changes seen during preeclampsia persist for years after preeclampsia.[69] Up to 10 years after preeclampsia, the prevalence of diastolic dysfunction, impaired left and right ventricular strain and subclinical (stage B) heart failure remain high at a relatively young age. In fact, the prevalence of aberrant cardiac LV remodelling is increased four times and heart failure is increased two-fold after preeclamptic pregnancy, with hypertension being the key determinant driving cardiac dysfunction.[65,67,70] These changes may not always be reversible and may persist or deteriorate, especially in persistent concomitant CV risk factors and comorbidities and may contribute to elevated risk for CVD.

## Concomitant cardiovascular risk factors and comorbidities

### Chronic hypertension

The development of chronic hypertension after pregnancies complicated by preeclampsia explains partly the increased risk of subsequent heart failure.[55] The cumulative incidence of hypertension at 10 years was 10% in women aged 20–29 years, which is higher than in women aged 40–49 years with a previous normotensive pregnancy.[71] A meta-analysis of post-natal hypertension showed that the odds ratio of postpartum hypertension was 5.42 (95% confidence interval [CI] 3.12–9.41) in the period up to 1 year and 7.24 (95% CI 4.44–11.80) between 1 to 2 years after HDP.[72]

### Atherosclerotic disease

Placental decidual vasculopathy in preeclampsia has a similar pathophysiological process to atherosclerosis, leading to the hypothesis that preeclampsia could induce development of systematic atherosclerosis at an accelerated rate.[73] Computed tomography angiography has demonstrated subclinical coronary atherosclerosis in 30% of reproductive age women consistent with a systematic review showing a 50% increase in CAD.[74,75] There is also a 40% increased risk of developing a stroke and a six-fold increased risk for vascular dementia following preeclampsia.[76] Also, follow-up for the Framingham Heart Study showed women with preeclampsia had higher risk of stroke later in life compared to women without preeclampsia (relative risk 3.79, 95% CI 1.24–11.60).[77]

### Renal dysfunction

Moreover, there is a five-fold increase in the risk of developing end-stage renal disease after preeclapmsia.[78] In contrast, there are less data on the development of chronic kidney disease (CKD) with one study showing a four-fold increase in risk for hypertensive/diabetic CKD and a two-fold increase for glomerular/proteinuric CKD at 20 years following preeclampsia.[78]

## Management strategies for hypertensive disorders of pregnancy

### Prepartum and intrapartum management

#### Screening and prevention

Women should be screened for CV risk factors associated with development of HDP including prior adverse pregnancy outcome, obesity, chronic hypertension, diabetes, collagen vascular disease, assisted reproductive technology, congenital heart disease, SDOH and ethnicity. When risk factors are present, women should be informed of increased HDP risk. Chronic hypertension or diabetes should be treated prior to pregnancy and lifestyle interventions pursued. Medications may need to be adjusted to avoid those with risk of teratogenicity or medication discontinuation if pregnancy occurs (*Tables* 2 and 3). Epidemiological studies suggest that healthy dietary patterns up to 3 years prior to pregnancy are associated with lower risks of HDP.[79] Weight management may also be effective. In a review of studies published between 1998 and 2005 addressing pregnancy following bariatric surgery, maternal complications, including HDP, appeared lower following surgically induced weight loss than in obese women without surgery approaching community rates.[80] A meta-analysis of 60 trials suggested low-dose aspirin for patients with ≥1 high risk factor for HDP or ≥2 moderate risk factors for HDP and considered with 1 moderate risk factor[81,82] However, more targeted use of aspirin prophylaxis on the basis of first trimester multiparameter screening has been shown to be superior to a risk factor-based approach with a 62% reduction in preterm preeclampsia.[83] Lifestyle interventions may also be useful including exercise, Mediterranean diet, and supplementation of calcium in the setting of low baseline intake.[84–86]

#### Multidisciplinary approach and pharmacological intervention

Optimal management of HDP requires collaboration between obstetricians, internal medicine specialists, cardiologists and general practitioners since guidelines for diagnosis and therapy are evolving and recommendations for therapy vary across societies. Beta-blockers, a first-line therapy option, have been suspected to impair foetal growth. However, in the CHAP study, an open-label randomized controlled trial on antihypertensive therapy with a goal BP of <140/90 mmHg in patients with non-severe chronic hypertension, treatment reduced the frequency of adverse outcomes without increasing the frequency of intrauterine growth retardation in all except those with severe obesity.[87] In this study, women enrolled prior to 24 weeks of gestation derived the most benefit.[87] Based on these findings, the ACOG supports implementing therapy

**Table 2 Antihypertensive medications in pregnancy**

| | Urgent control for severe hypertension |
|---|---|
| **First-line agents for pregnancy for chronic hypertension/gestational hypertension (starting to maximum dose)** | |
| Labetalol<br>200–2400 mg daily in divided doses | 20 mg i.v. over 2 min<br>Subsequent up-titration at 10-min intervals if BP not controlled to maximum dose of 300 mg; hold for HR < 60 bpm. |
| Nifedipine, extended release<br>30–120 mg daily | Dihydropyridine calcium channel blocker options include: nifedipine, extended release 30 mg, immediate release 10 mg, or i.v. nicardipine continuous drip beginning at 5 mg i.v. per hour |
| Alpha-methyldopa<br>250–3000 mg daily in divided doses<br>Discontinue postpartum: associated with increased depression risk | Not used |
| Hydralazine<br>40–200 mg daily in divided doses | 5 mg i.v. gradually over 1 to 2 min.<br>Adequate reduction of BP is less predictable than with i.v. labetalol |
| **Second-line agents for pregnancy for chronic hypertension/gestational hypertension (starting to maximum dose)** | |
| Clonidine 0.1–0.6 mg bid<br>0.1–0.6 mg transdermal weekly | |
| **Antihypertensive for use postpartum in lactating patients** | |
| Beta-blockers | Metoprolol, labetalol, propranolol preferred |
| ACE-inhibitors | Captopril, enalapril, benazepril, quinapril preferred |
| Dihydropyridine calcium channel blockers | Nifedipine/amlodipine acceptable |
| Diuretics | Generally considered safe, although theoretic concern of decrease breast milk production |
| MRA | Spironolactone generally considered safe |

ACE, angiotensin-converting enzyme; BP, blood pressure; HR, heart rate; i.v., intravenous; MRA, mineralocorticoid receptor antagonist.

**Table 3 Antihypertensive medications to be avoided in pregnancy**

| Agent | Potential fetal effect |
|---|---|
| ACE-inhibitors | Teratogenicity and foetal death |
| Angiotensin receptor blockers | Teratogenicity and foetal death |
| Renin inhibitors | Teratogenicity and foetal death |
| Mineralocorticoid receptor antagonists | Anti-androgenic effects, feminization of male foetuses |

ACE, angiotensin-converting enzyme.

with a BP of >140/90 mmHg (*Figure 4*).[25] Whether this translates to prevention of CVD in later life is not yet known.

### Tailored blood pressure management to improve obstetric outcome

Earlier disappointing effects of antihypertensive medication can be anticipated when the pharmacological mode of action does not match the underlying haemodynamic imbalance. In fact, hypertension in pregnancy may result from (i) high cardiac output, low vascular resistance state, in which beta-blockade is expected to be most effective, or (ii) low cardiac output, high vascular resistance state where dihydropyridine calcium channel blockers or central-acting alpha agonists might be the best corrective medication. In the latter, beta-blockade might be maternally ineffective and even contribute to impaired foetal growth by keeping cardiac output low. A recent study showed that tailored circulatory normalization of non-physiological haemodynamic changes during pregnancy halves the risk of recurrent preeclampsia, without disadvantageous effects on offspring outcome.[88]

## Early postpartum management

Patients with preeclampsia should not be candidates for discharge until BP has stabilized. Subsequent follow-up should occur no later than 7–10 days post-delivery.[89] ACOG recommends frequent monitoring of BP postpartum. Treatment with furosemide for 5 days has been shown to speed resolution of postpartum hypertension.[90] ACOG suggests initiation of antihypertension therapy for BP ≥150/100 mmHg on two occasions at least 4–6 h apart.[91] However, in a retrospective analysis, therapy initiation at lower threshold of ≥140/90 mmHg would reduce postpartum admissions.[92] A significant proportion of patients develop preeclampsia postpartum. Many will not have a history of antepartum preeclampsia and may not demonstrate classic features such as oedema, proteinuria or hyperreflexia underlining the importance of a high index of suspicion.

Lactation has favourable effects on cardiometabolic profiles resulting in lower fasting blood glucose, improved lipid profiles, insulin resistance and BP. In the CARDIA study, longer duration of breastfeeding in women 18–30 years old was associated with higher high-density lipoprotein cholesterol levels, lower rates of type 2 diabetes and lower risk of hypertension or early atherosclerosis.[93] In the Black Women's Health Study longer duration of

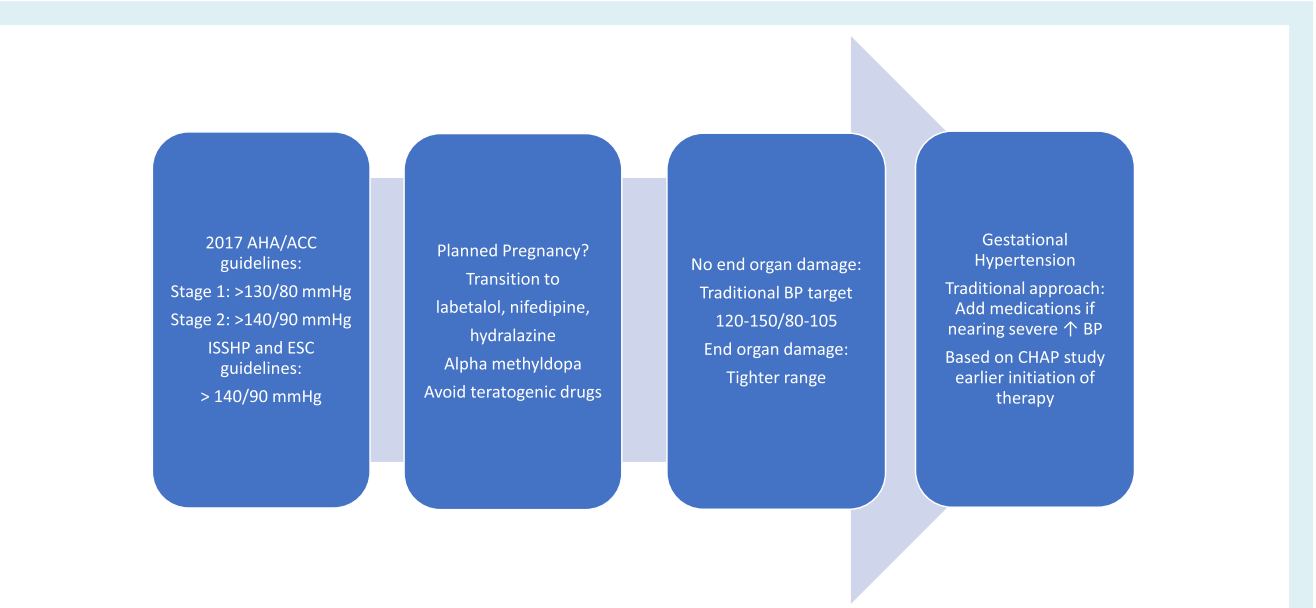



**Figure 4** Approach to hypertension in pregnancy. Different societies vary in definition of chronic hypertension. AHA/ACC 2017 guidelines define Stage 1 hypertension as >130/80 mmHg and Stage 2 as >140/90 mmHg. ISSHP and ESC 2018 define hypertension as >140/90 mmHg. Women with chronic hypertension planning pregnancy should consider transitioning to a medication safe with pregnancy. For women without evidence for end-organ damage traditional target goals for therapy are reasonable. In presence of end-organ damage, tighter control is recommended. For women developing gestational hypertension, traditionally medication is started if blood pressure (BP) nears severe range. Based on the recent CHAP study,[87] earlier therapy initiation should be considered.

breastfeeding was associated with less hypertension in middle age (40–49 years), but not at older age.[94]

## Remote postpartum management

Traditionally, the first postpartum visit is at 6 weeks with an obstetrician. A newer approach includes early follow-up with at BP check at 3–10 days, high risk follow-up at 1–3 weeks and comprehensive postpartum follow-up with CV screen and transition to well adult care at 4–12 weeks.[89] The SNAP-HT randomized controlled trial compared remote self-management to usual care following preeclampsia.[95] The results demonstrated that BP control was better whilst on remote self-management with the difference most marked at 6 weeks. However, another striking finding was that diastolic BP was significantly lower at 6 months and 4 years postpartum in those randomized to postpartum BP self-management versus those treated with standard care. There is an optimal window to ameliorate long-term CVD risk in the puerperium and if the diastolic BP difference were to be maintained long term, it correlates to a 40% lifetime reduction in stroke and 20% lifetime reduction in CAD risk.[96] A randomized double-blind placebo-controlled feasibility trial of enalapril following early-onset preeclampsia showed no difference in the primary outcome (total vascular resistance) at 6 months postpartum. However, women treated with enalapril had significantly better diastolic function at 6 months than those treated with placebo. Enalapril use was also associated with improved LV remodelling at 6 months and improvement in diastolic BP in the intervention arm.[15]

### Postpartum screening for cardiovascular risk

Candidates for screening and recommendations are shown in *Figures 5* and *6*. Unfortunately for many, a pregnancy history is not uniformly obtained and development of incident hypertension and other CV risk factors may be missed.[97,98] Novel approaches to improve patient participation include maternal health clinics, use of ancillary support services (Doulas/Cocoon clinics), telehealth visits, text messaging support for BP monitoring and diabetes screening.[90,99–102]

### Prediction models for postpartum cardiovascular dysfunction

The inclusion of a history of preeclampsia in an established CV risk score does not substantially improve discrimination or reclassification of CVD risk prediciton.[103–105] Current CVD risk calculators have not been designed for women of reproductive age who have a low CVD risk, highlighting the urgent need to develop models to assess long-term CVD risk which include sex-specific risk factors such as HDP. To achieve this, it might be helpful to target prediction of CV risk factors such as hypertension, diabetes, and dyslipidaemia instead of CVD that occurs several decades after preeclampsia. Indeed, hypertension and obesity are essential targets for CV prevention in women after preeclampsia.[106] The key management strategy is to recognize that HDP predicts subsequent CVD earlier than traditional risk factors providing an opportunity for intensive primary prevention. This requires identification of women at risk, aggressive treatment of CV risk factors,

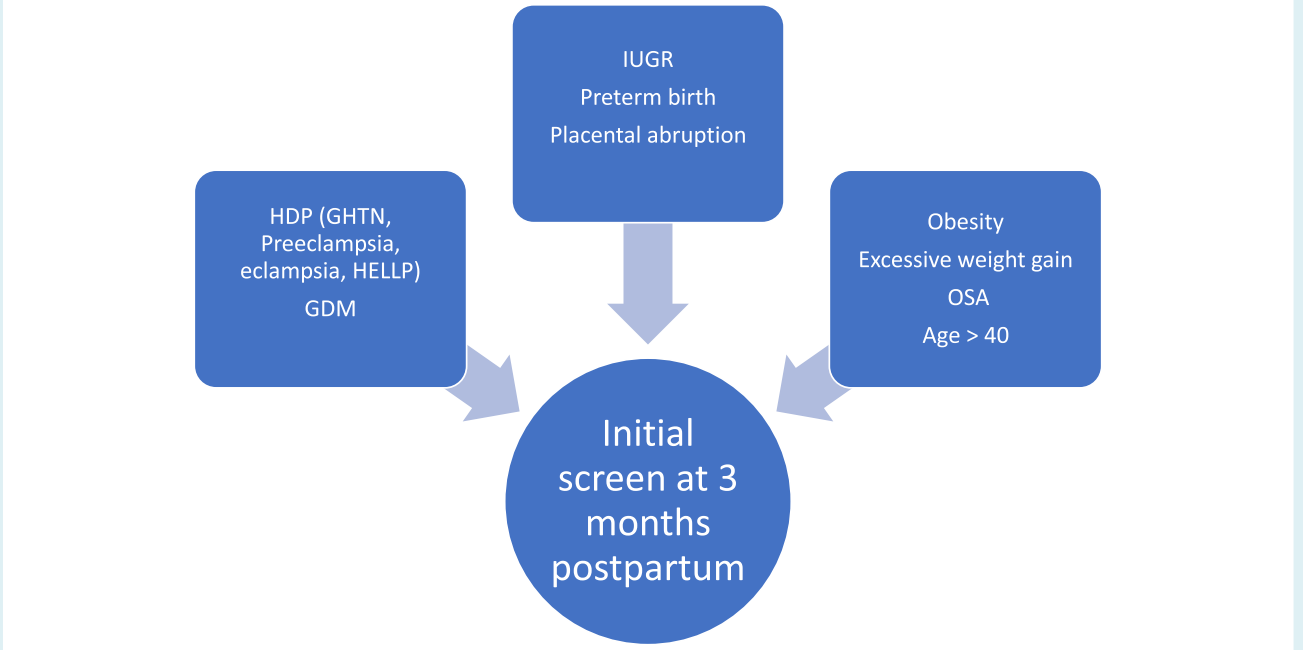



**Figure 5** Who should we screen after hypertensive pregnancy? Patients who may benefit from screening and primary prevention. Any patient with hypertensive disorders of pregnancy (HDP), including gestational hypertension (GHTN), preeclampsia, eclampsia or HELLP syndrome (haemolysis, elevated liver enzymes, low platelet count). Patients with gestational diabetes mellitus (GDM), intra-uterine growth restriction (IUGR), preterm birth or placental abruption, obesity, excessive weight gain with pregnancy, obstructive sleep apnoea (OSA) or age >40 years.

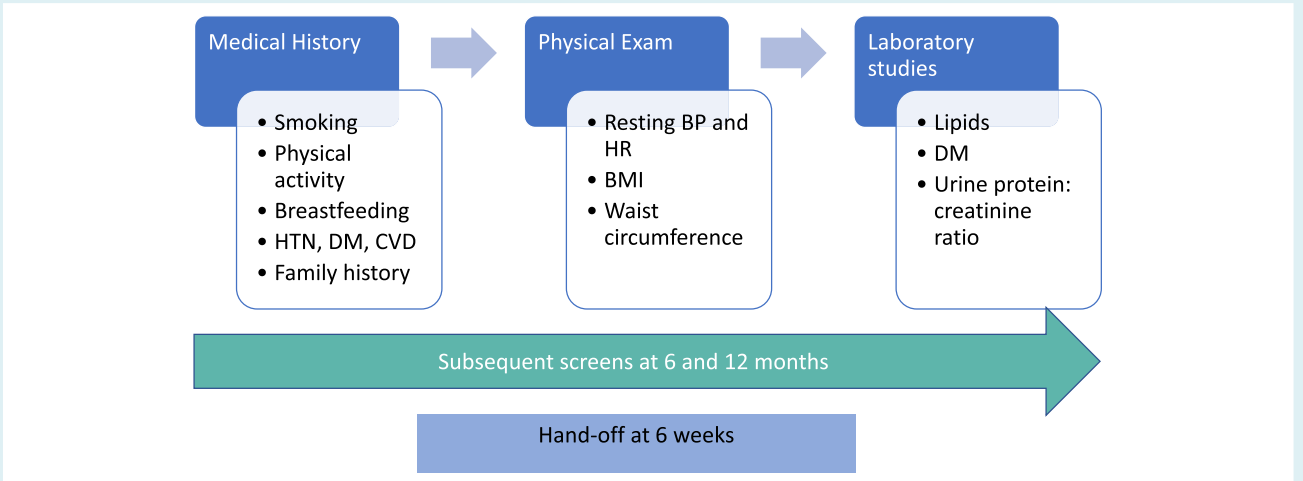



**Figure 6** How should we screen women after hypertensive disorders of pregnancy ? Screening considerations for women with hypertensive disorders of pregnancy. A general cardiovascular risk assessment should be made of women with hypertensive disorders of pregnancy. The transfer of care to well prevention from obstetrics and gynaecology typically occurs by 6 weeks. Subsequent screening performed at 6 and 12 months. This should include usual risk factors for cardiovascular disease (CVD) including prior cardiovascular events, presence of chronic hypertension (HTN), diabetes mellitus (DM), smoking, physical inactivity, family history of CVD, mitigating factors such as breast feeding, physical parameters (body mass index [BMI], blood pressure [BP], waist circumference) and laboratory parameters including lipids, glucose/glycated haemoglobin and urine protein/creatinine ratio. HR, heart rate.

multidisciplinary care, improved care access, attention to SDOH and novel approaches to care delivery.[106] Recently, two prediction model for remote chronic hypertension and aberrant cardiac remodelling after preeclampsia have been developed. These prediction models are based on easily available clinical indices and still need to be implemented in clinical guidelines and practices.[107,108]

## Future perspectives

Although HDP has an immediate and detrimental impact on maternal CV health than previously known, no structural CV follow-up programmes after these high-risk pregnancies have been implemented. Guidelines recognize preeclampsia as an early indicator of CVD risk and advise appropriate follow-up after pregnancy for monitoring and control of CVD risk factors but remain vague about specific strategies to do this. Structural longitudinal CV assessment of all women after HPD would implicate a novel additional burden on healthcare facilities, as it would mean screening around 5–10% of all former pregnant women. As not all women with HPD have high risk for CVD, unselected longitudinal follow-up screening of all women would result in over medicalization for a large proportion of them. A possible effective strategy to meet the clinical care demand and being purposeful at the same time may be structured analysis of all women after HPD in the first year after delivery along with personalized CV risk modelling and suited individualized CV risk management. Although the exact modality of screening and protocol of intervention has not been standardized, mainly due to limited available evidence-based clinical research on antenatal and postnatal care, recent evidence suggests a potential role for early BP control with angiotensin-converting enzyme inhibitors.[15] Whether this will result in improved reverse remodelling and prevention of heart failure is subject for future research. Nevertheless, encouraging weight control, stop smoking, healthy diet, and daily exercise are all well-established and cost-effective prevention strategies and should be implemented in regular clinical care.

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