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Cardiac Target Organ Damage in Hypertension: Insights from Epidemiology

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Abstract

Hypertension is an important risk factor implicated in the development of multiple common cardiac conditions, including coronary atherosclerosis, heart failure, and atrial fibrillation. Epidemiologic studies have provided insight into the shared pathogenesis of hypertension and subclinical as well as clinically evident cardiac diseases. The mechanistic common ground between chronic blood pressure elevation and cardiac disease likely begins early in life. Understanding these connections will aid ongoing efforts to identify individuals at risk, develop targeted therapeutics, and improve overall outcomes for individuals with elevated blood pressure in the population at large.

Keywords

Blood pressure; hypertension; cardiac disease; epidemiology

Introduction

Given the magnitude of cardiac risk associated with hypertension, and its wide prevalence in the community at large, hypertension remains among the most important modifiable risk factors for cardiac disease. Specifically, hypertension significantly augments risk for major morbid and common cardiac conditions such as coronary atherosclerosis, heart failure, and atrial fibrillation. Globally, it is estimated that 7.6 million premature deaths and 92 million disability-adjusted life years are attributed to elevated blood pressure (BP).¹ As the world population ages, the prevalence of hypertension and its end-organ sequelae will only continue to increase. Decades of epidemiologic investigations have helped to identify key determinants of hypertension-related cardiac disease and, in turn, highlighted treatment opportunities. Herein, we will review the insights that epidemiologic observations have

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provided to date regarding the progression from hypertension to subclinical and eventual clinical cardiac disease.

Precursors to Hypertension

Numerous risk factors for hypertension are also risk factors for cardiac disease, suggesting shared pathophysiology (Figure 1). It is well known that clinical traits such as older age, male sex, greater body mass index, parental history of hypertension, and cigarette smoking are all associated with increased risk for both incident hypertension and developing an adverse cardiac event.² Several emerging biomarkers have also been associated with both hypertension and overt cardiac disease, underscoring mechanistic common ground. Specifically, biomarker investigations have implicated pathways of inflammation (C-reactive protein), thrombosis (fibrinogen), fibrinolytic potential (plasminogen activator inhibitor-1), neurohormonal activity (aldosterone, renin, B-type natriuretic peptide [BNP], and N-terminal proatrial natriuretic peptide), and oxidative stress (homocysteine) in association with both subsequent hypertension³ and heart failure;⁴ many of these same biomarkers have been shown to predict a first major cardiovascular event and death.⁵

Epidemiologic investigations into the origins of hypertension and associated cardiac disease have also identified common genetic traits that may precede and possibly manifest as detectable variations in pathway biomarkers. Intriguingly, certain conserved DNA variants that are associated with the development of hypertension are also associated with several overt cardiac conditions, including left ventricular hypertrophy (LVH) and coronary atherosclerosis.^{6–8} Notably, these variants include polymorphisms at distinct loci encoding for natriuretic peptides, subunits of soluble guanylate cyclase, and adrenomedullin in addition to several other proteins with biologically plausible effects on BP regulation. Hence, the pathway to cardiac disease in many individuals with hypertension likely begins well before the onset of elevated BP.

Progression from Hypertension to Subclinical Cardiac Disease

The progression from chronically elevated BP, once established, towards overt cardiac disease often involves initially asymptomatic alterations in cardiac structure and function. Subclinical abnormalities in cardiac structure are associated with abnormalities at the cellular level, including cardiomyocyte hypertrophy, dropout, and replacement fibrosis. Gross morphologic manifestations include the development of left ventricular remodeling, with or without an increase in LV mass. Longitudinal cohort data indicate that age-related cardiac remodeling over the adult life course includes a progressive increase in LV wall thickness (concentric remodeling) and a concomitant decrease in LV dimensions (cavity shrinkage).^{9,10} Elevations in BP are also associated with these structural abnormalities and, in addition to augmenting so-called age-related cardiac remodeling, promote the development of concentric hypertrophy in particular.^{10,11} Thus, the most well-recognized structural phenotype of hypertensive heart disease is LVH, defined as an increase in LV mass, and involving more often an increase in wall thickness than an increase in LV cavity size.¹²

Interestingly, the development of LVH can occur very early in life, even in adolescence¹³ and prior to a clinical diagnosis of hypertension.¹⁴ Mechanistic contributors to both hypertension and LVH may involve angiotensin II,¹⁵ endothelin,^{16–18} the circulating catecholamines (norepinephrine and epinephrine), and increased sympathetic tone involving both peripheral and cardiac efferents.^{19,20} Genetic traits that predispose to both hypertension and LVH have also been identified, including deletion polymorphisms in genes such as the angiotensin-converting enzyme (ACE) and the bradykinin 2 receptor (B2BKR 2).^{21,22} Conventional and novel biomarkers of cardiac stress have been associated with LVH as well as LV systolic dysfunction; these biomarkers include growth differentiation factor-15 (GDF-15) and BNP, both of which have also been related to arterial remodeling and dysfunction.^{23–25} Clinical factors substantially influence the relationship between hypertension and LVH. For example, hypertensive women exhibit a greater prevalence of LVH than men for a similar degree of BP elevation, and less regression of LVH with antihypertensive therapy;²⁶ this finding is also observed in blacks compared to whites.^{27–29}

Hypertension is related not only to subclinical abnormalities in cardiac structure but also function. Although chronically elevated BP may eventually lead to a reduced LV ejection fraction (LVEF),³⁰ often in the setting of eccentric hypertrophy, the more common and much earlier manifestations of BP-related cardiac dysfunction include abnormalities in LV diastolic function, ventricular-vascular coupling, and myocardial strain – all typically in the presence of a preserved LVEF. Asymptomatic diastolic dysfunction is prevalent in up to 25% of adults in the community, especially in the setting of hypertension and particularly in the setting of elevated systolic BP.^{31–33} Mechanistically, abnormal vascular stiffness has been observed in association with reduced ventricular elastance (the substrate for diastolic dysfunction) with an apparent predilection for older adults and women.^{34,35} This interactive coupling of ventricular-vascular abnormalities may be especially relevant for individuals predisposed to HF with preserved LVEF.³⁶ Several studies have demonstrated that elevated BP is associated with abnormalities in LV strain,^{37,38} reflecting alterations in myocardial systolic deformation even in the setting of a normal LVEF. Notably, abnormalities in subclinical LV global and regional strain as well as synchrony have been associated specifically with LVH in addition to hypertension.^{39,40}

Progression from Subclinical to Clinical Cardiac Disease

Among individuals with asymptomatic hypertensive heart disease, many will go on to develop the familiar cardiac sequelae of hypertension including coronary artery disease (CAD), heart failure (HF) with and without a preserved LVEF, and common arrhythmias such as atrial fibrillation. The progression from subclinical to clinical cardiac disease may be influenced by multiple factors including the type of BP elevation (e.g. isolated systolic, isolated diastolic, or combined hypertension), severity of BP elevation, duration of BP elevation, presence of concomitant risk factors, and treatment exposure.

The most common clinical cardiac disease that occurs in hypertensive individuals is atherosclerotic CAD, with elevated BP contributing to almost half of all coronary events.¹ Large, mainly population-based studies have clearly identified hypertension as an independent risk factor for CAD.^{41–50} A meta-analysis of observational studies involving

one million hypertensive individuals, representing 12.7 million person-years at risk, showed that BP elevations above a threshold as low as 115/75 mmHg were associated CAD.⁵¹ The investigators reported that between ages 40 to 69 years of age, each systolic BP difference of 20 mm Hg or diastolic BP difference of 10 mm Hg was associated with a twofold increase in the mortality rates from CAD as well as from other vascular causes. These associations are even more pronounced in older adults.⁵² Interestingly, CAD has been observed as the first cardiovascular event to occur after hypertension onset in men, whereas stroke tends to be the first event after hypertension onset in women.⁵³ The various hemodynamic loading conditions manifesting as different forms of hypertension may also play a role, as data from some cohorts suggest that systolic BP may be a particularly important determinant of CAD risk when compared to diastolic or mean BP.⁵⁴ Mechanistically, chronically elevated BP of any type is believed to increase the rate at which atherogenic lipid molecules are taken up into vascular plaque due to increases in transmural pressure in arterial vessels and an increase in mechanical stress and endothelial permeability.⁵⁵ Abnormal endothelial function and abnormal nitric oxide signaling may also play a role.^{56,57} Importantly, BP lowering therapy is efficacious in both the primary and secondary prevention of CAD.⁵⁸ In a meta-analysis of nearly 464,000 participants from 147 clinical trials, there was a 22% reduction in coronary events for a systolic BP reduction of 10 mm Hg or diastolic of 5 mm Hg,⁵⁸ mirroring data from observational studies that had previously indicated equivalent BP reductions in association with a 25% decrease in CAD risk.⁵¹

Whereas CAD is the most common cardiac disease that occurs in hypertensives, hypertension is by far the most prevalent major risk factor among individuals who develop HF.⁵⁹ Indeed, the coexistence of hypertension and CAD markedly increases HF risk, likely through neurohormonal activation and promotion of early ventricular remodeling.⁶⁰ Nonetheless, while CAD is also a well-recognized risk factor for HF, CAD is not a part of the causal pathway between hypertension and HF in a majority of cases. Early evidence suggested that the hypertension coinciding with CAD tends to lead to HF with reduced EF (HFREF), whereas the hypertension existing in the absence of CAD tends to lead to HF with preserved EF (HFPEF). However, more recent population-based data indicate that this distinction is not so clear, and that hypertension likely plays an important role in increasing risk for both these types of HF.^{61,62} Duration of BP exposure likely impacts the overall risk for HF, and the timing of hypertension onset (i.e. during mid-life) also appears to be important.⁶³ Data from several studies indicate that hypertension after age 40 years doubles the risk of incident systolic HF, and even mild elevations in BP are associated with increased risk overall.^{59,64–66} Cohort data also suggest that elevations in systolic BP and pulse pressure may be more hemodynamically important determinants of systolic HF than elevations in diastolic or mean BP.⁶⁷ These findings coincide with physiologic studies indicating that interactive coupling of arterial and LV stiffness may play a particularly important role in the development of HFPEF as well as HFREF.^{36,68} In addition to arterial stiffness,⁶⁹ the intermediate phenotypes of subclinical cardiac disease that are commonly associated with hypertension, including LVH and conventionally defined asymptomatic LV systolic as well as diastolic dysfunction, have all been shown to increase HF risk in the community.^{30,70–72}

Notwithstanding CAD and HF, hypertension is also the most important modifiable risk factor for the most common cardiac arrhythmia, non-valvular atrial fibrillation (AF).^{73–76} Data from large cohort studies indicate that hypertension increases the risk of AF by 40–50%.^{77,78} Population-based studies also suggest that the risk of incident AF among patients treated for hypertension differs by the degree of BP control, with declining rates of incident AF among those hypertensive patients treated closer to a pre-specified target.⁷⁹ Anti-hypertensive therapies that target the renin-angiotensin-aldosterone axis may have particular utility.⁷⁶ Mechanistically, the cardiac structural and functional abnormalities that accompany hypertension – LVH, impaired ventricular filling, left atrial enlargement – are associated with a slowing of atrial conduction velocity, which favors the development of atrial fibrillation.^{74,80}

Conclusions

Epidemiologic studies to date indicate that the transition from hypertension to heart disease is a process that typically progresses over the life course – and that the pathogenesis likely begins very early in life. The classic paradigm is that, in vulnerable individuals, hypertension initially leads to subclinical disease that can manifest with abnormalities in imaging as well as non-imaging biomarkers of cardiac stress and end-organ damage, prior to the onset of clinically overt outcomes. However, this pattern of progression proves not always to be the case. Hypertension is, in fact, a heterogeneous disorder and modifying exposures are not always captured. In addition, many forms of subclinical cardiac disease are not completely detected using conventional methods and assays, which may have limited sensitivity for detecting subtle incremental changes. Moreover, even among individuals with obvious subclinical cardiac remodeling and dysfunction, not all will go on to develop symptomatic disease. Further research is needed to clarify why it is that many people with hypertension go on to develop events and, equally as important, why many people with hypertension do not – with or without the chronic administration of conventional BP lowering therapies. Given the wide and growing prevalence of hypertension in the community at large, investigating the precursor and preclinical determinants of hypertensive heart disease remains an important area of ongoing research.

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REFERENCES

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Lawes CM, Vander Hoorn S, Rodgers A. Global burden of blood-pressure-related disease, 2001. *Lancet*. 2008; 371:1513–1518. [PubMed: 18456100] • This study illustrates the scope of the hypertension problem worldwide, and underscores the far-reaching and multi-national implications of this global pandemic.

2. Echouffo-Tcheugui JB, Batty GD, Kivimaki M, Kengne AP. Risk models to predict hypertension: A systematic review. *PLoS One*. 2013; 8:e67370. [PubMed: 23861760]
3. Wang TJ, Gona P, Larson MG, Levy D, Benjamin EJ, Tofler GH, Jacques PF, Meigs JB, Rifai N, Selhub J, Robins SJ, Newton-Cheh C, Vasani RS. Multiple biomarkers and the risk of incident hypertension. *Hypertension*. 2007; 49:432–438. [PubMed: 17242302]
4. Velagaleti RS, Gona P, Larson MG, Wang TJ, Levy D, Benjamin EJ, Selhub J, Jacques PF, Meigs JB, Tofler GH, Vasani RS. Multimarker approach for the prediction of heart failure incidence in the community. *Circulation*. 2010; 122:1700–1706. [PubMed: 20937976]
5. Wang TJ, Gona P, Larson MG, Tofler GH, Levy D, Newton-Cheh C, Jacques PF, Rifai N, Selhub J, Robins SJ, Benjamin EJ, D'Agostino RB, Vasani RS. Multiple biomarkers for the prediction of first major cardiovascular events and death. *N Engl J Med*. 2006; 355:2631–2639. [PubMed: 17182988]
6. Levy D, Ehret GB, Rice K, Verwoert GC, Launer LJ, Dehghan A, Glazer NL, Morrison AC, Johnson AD, Aspelund T, Aulchenko Y, Lumley T, Kottgen A, Vasani RS, Rivadeneira F, Eiriksdottir G, Guo X, Arking DE, Mitchell GF, Mattace-Raso FU, Smith AV, Taylor K, Scharpf RB, Hwang SJ, Sijbrands EJ, Bis J, Harris TB, Ganesh SK, O'Donnell CJ, Hofman A, Rotter JJ, Coresh J, Benjamin EJ, Uitterlinden AG, Heiss G, Fox CS, Witteman JC, Boerwinkle E, Wang TJ, Gudnason V, Larson MG, Chakravarti A, Psaty BM, van Duijn CM. Genome-wide association study of blood pressure and hypertension. *Nat Genet*. 2009; 41:677–687. [PubMed: 19430479]
7. Ehret GB, Munroe PB, Rice KM, Bochud M, Johnson AD, Chasman DI, Smith AV, Tobin MD, Verwoert GC, Hwang SJ, Pihur V, Vollenweider P, O'Reilly PF, Amin N, Bragg-Gresham JL, Teumer A, Glazer NL, Launer L, Zhao JH, Aulchenko Y, Heath S, Sober S, Parsa A, Luan J, Arora P, Dehghan A, Zhang F, Lucas G, Hicks AA, Jackson AU, Peden JF, Tanaka T, Wild SH, Rudan I, Igl W, Milaneschi Y, Parker AN, Fava C, Chambers JC, Fox ER, Kumari M, Go MJ, van der Harst P, Kao WH, Sjogren M, Vinay DG, Alexander M, Tabara Y, Shaw-Hawkins S, Whincup PH, Liu Y, Shi G, Kuusisto J, Tayo B, Seielstad M, Sim X, Nguyen KD, Lehtimäki T, Matullo G, Wu Y, Gaunt TR, Onland-Moret NC, Cooper MN, Platou CG, Org E, Hardy R, Dahgam S, Palmen J, Vitart V, Braund PS, Kuznetsova T, Uitterwaal CS, Adeyemo A, Palmas W, Campbell H, Ludwig B, Tomaszewski M, Tzoulaki I, Palmer ND, Aspelund T, Garcia M, Chang YP, O'Connell JR, Steinle NI, Grobbee DE, Arking DE, Kardia SL, Morrison AC, Hernandez D, Najjar S, McArdle WL, Hadley D, Brown MJ, Connell JM, Hingorani AD, Day IN, Lawlor DA, Beilby JP, Lawrence RW, Clarke R, Hopewell JC, Ongen H, Dreisbach AW, Li Y, Young JH, Bis JC, Kahonen M, Viikari J, Adair LS, Lee NR, Chen MH, Olden M, Pattaro C, Bolton JA, Kottgen A, Bergmann S, Mooser V, Chaturvedi N, Frayling TM, Islam M, Jafar TH, Erdmann J, Kulkarni SR, Bornstein SR, Grassler J, Groop L, Voight BF, Kettunen J, Howard P, Taylor A, Guarrera S, Ricceri F, Emilsson V, Plump A, Barroso I, Khaw KT, Weder AB, Hunt SC, Sun YV, Bergman RN, Collins FS, Bonnycastle LL, Scott LJ, Stringham HM, Peltonen L, Perola M, Vartiainen E, Brand SM, Staessen JA, Wang TJ, Burton PR, Soler Artigas M, Dong Y, Snieder H, Wang X, Zhu H, Lohman KK, Rudock ME, Heckbert SR, Smith NL, Wiggins KL, Doumatey A, Shriner D, Veldre G, Viigimaa M, Kinra S, Prabhakaran D, Tripathy V, Langefeld CD, Rosengren A, Thelle DS, Corsi AM, Singleton A, Forrester T, Hilton G, McKenzie CA, Salako T, Iwai N, Kita Y, Ogiwara T, Ohkubo T, Okamura T, Ueshima H, Umemura S, Eyheramendy S, Meitinger T, Wichmann HE, Cho YS, Kim HL, Lee JY, Scott J, Sehmi JS, Zhang W, Hedblad B, Nilsson P, Smith GD, Wong A, Narisu N, Stancakova A, Raffel LJ, Yao J, Kathiresan S, O'Donnell CJ, Schwartz SM, Ikram MA, Longstreth WT Jr, Mosley TH, Seshadri S, Shrine NR, Wain LV, Morken MA, Swift AJ, Laitinen J, Prokopenko I, Zitting P, Cooper JA, Humphries SE, Danesh J, Rasheed A, Goel A, Hamsten A, Watkins H, Bakker SJ, van Gilst WH, Janipalli CS, Mani KR, Yajnik CS, Hofman A, Mattace-Raso FU, Oostra BA, Demirkan A, Isaacs A, Rivadeneira F, Lakatta EG, Orru M, Scuteri A, Ala-Korpela M, Kangas AJ, Lyytikäinen LP, Soininen P, Tukiainen T, Wurtz P, Ong RT, Dorr M, Kroemer HK, Volker U, Volzke H, Galan P, Hercberg S, Lathrop M, Zelenika D, Deloukas P, Mangino M, Spector TD, Zhai G, Meschia JF, Nalls MA, Sharma P, Terzic J, Kumar MV, Denniff M, Zukowska-Szczekowska E, Wagenknecht LE, Fowkes FG, Charchar FJ, Schwarz PE, Hayward C, Guo X, Rotimi C, Bots ML, Brand E, Samani NJ, Polasek O, Talmud PJ, Nyberg F, Kuh D, Laan M, Hveem K, Palmer LJ, van der Schouw YT, Casas JP, Mohlke KL, Vineis P, Raitakari O, Ganesh SK, Wong TY, Tai ES, Cooper RS, Laakso M, Rao DC, Harris TB, Morris RW, Dominiczak AF, Kivimäki M, Marmot MG, Miki T, Saleheen D, Chandak GR, Coresh J, Navis G, Salomaa V, Han BG, Zhu X, Kooner JS, Melander O, Ridker PM, Bandinelli S, Gyllenstein UB, Wright AF, Wilson JF, Ferrucci L, Farrall

M, Tuomilehto J, Pramstaller PP, Elosua R, Soranzo N, Sijbrands EJ, Altshuler D, Loos RJ, Shuldiner AR, Gieger C, Meneton P, Uitterlinden AG, Wareham NJ, Gudnason V, Rotter JI, Rettig R, Uda M, Strachan DP, Witteman JC, Hartikainen AL, Beckmann JS, Boerwinkle E, Vasan RS, Boehnke M, Larson MG, Jarvelin MR, Psaty BM, Abecasis GR, Chakravarti A, Elliott P, van Duijn CM, Newton-Cheh C, Levy D, Caulfield MJ, Johnson T. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature*. 2011; 478:103–109. [PubMed: 21909115] • This large genome-wide association study of systolic and diastolic blood pressure used a multi-stage design in 200,000 individuals of European descent to identify sixteen novel loci associated with prevalent hypertension. Six of these loci harbored genes previously known or postulated to regulate BP (GUCY1A3–GUCY1B3, NPR3–C5orf23, ADM, FURIN–FES, GOSR2, GNAS–EDN3). Intriguingly, the other 10 were not previously implicated in BP regulation, and therefore provide insight into potential novel pathways.

8. Schnabel RB. Common genetic variation of blood pressure traits and their relation to end-organ damage. *Circ Cardiovasc Genet*. 2011; 4:712–713. [PubMed: 22187451]
9. Cheng S, Fernandes VR, Bluemke DA, McClelland RL, Kronmal RA, Lima JA. Age-related left ventricular remodeling and associated risk for cardiovascular outcomes: The Multi-Ethnic Study of Atherosclerosis. *Circ Cardiovasc Imaging*. 2009; 2:191–198. [PubMed: 19808592]
10. Cheng S, Xanthakis V, Sullivan LM, Lieb W, Massaro J, Aragam J, Benjamin EJ, Vasan RS. Correlates of echocardiographic indices of cardiac remodeling over the adult life course: Longitudinal observations from the Framingham Heart Study. *Circulation*. 2010; 122:570–578. [PubMed: 20660804] • This study followed individuals in the Framingham Heart Study for asymptomatic progressive cardiac remodeling. The investigators showed that with advancing age, patterns of increasing LV wall thickness, decreasing LV dimensions, and increasing fractional shortening emerge. Hypertension, along with female sex and diabetes mellitus, influenced this pattern of remodeling.
11. Lieb W, Xanthakis V, Sullivan LM, Aragam J, Pencina MJ, Larson MG, Benjamin EJ, Vasan RS. Longitudinal tracking of left ventricular mass over the adult life course: Clinical correlates of short- and long-term change in the framingham offspring study. *Circulation*. 2009; 119:3085–3092. [PubMed: 19506113]
12. Drazner MH. The progression of hypertensive heart disease. *Circulation*. 2011; 123:327–334. [PubMed: 21263005]
13. Daniels SD, Meyer RA, Loggie JM. Determinants of cardiac involvement in children and adolescents with essential hypertension. *Circulation*. 1990; 82:1243–1248. [PubMed: 2401062]
14. Post WS, Larson MG, Levy D. Impact of left ventricular structure on the incidence of hypertension. The Framingham Heart Study. *Circulation*. 1994; 90:179–185. [PubMed: 8025994]
15. Mazzolai L, Nussberger J, Aubert JF, Brunner DB, Gabbiani G, Brunner HR, Pedrazzini T. Blood pressure-independent cardiac hypertrophy induced by locally activated reninangiotensin system. *Hypertension*. 1998; 31:1324–1330. [PubMed: 9622149]
16. Masaki T, Kimura S, Yanagisawa M, Goto K. Molecular and cellular mechanism of endothelin regulation. Implications for vascular function. *Circulation*. 1991; 84:1457–1468. [PubMed: 1655302]
17. Ichikawa KI, Hidai C, Okuda C, Kimata SI, Matsuoka R, Hosoda S, Quertermous T, Kawana M. Endogenous endothelin-1 mediates cardiac hypertrophy and switching of myosin heavy chain gene expression in rat ventricular myocardium. *J Am Coll Cardiol*. 1996; 27:1286–1291. [PubMed: 8609357]
18. Hua L, Li C, Xia D, Qu P, Li Z, Zhang W, Feng X. Relationship between hypertensive left ventricular hypertrophy and levels of endothelin and nitric oxide. *Hypertens Res*. 2000; 23:377–380. [PubMed: 10912776]
19. Schlaich MP, Kaye DM, Lambert E, Sommerville M, Socratous F, Esler MD. Relation between cardiac sympathetic activity and hypertensive left ventricular hypertrophy. *Circulation*. 2003; 108:560–565. [PubMed: 12847071]
20. Greenwood JP, Scott EM, Stoker JB, Mary DA. Hypertensive left ventricular hypertrophy: Relation to peripheral sympathetic drive. *J Am Coll Cardiol*. 2001; 38:1711–1717. [PubMed: 11704385]

21. Schunkert H, Hense HW, Holmer SR, Stender M, Perz S, Keil U, Lorell BH, Riegger GA. Association between a deletion polymorphism of the angiotensin-converting-enzyme gene and left ventricular hypertrophy. *N Engl J Med*. 1994; 330:1634–1638. [PubMed: 8177269]
22. Brull D, Dhamrait S, Myerson S, Erdmann J, Woods D, World M, Pennell D, Humphries S, Regitz-Zagrosek V, Montgomery H. Bradykinin b2br receptor polymorphism and left-ventricular growth response. *Lancet*. 2001; 358:1155–1156. [PubMed: 11597672]
23. Xanthakis V, Larson MG, Wollert KC, Aragam J, Cheng S, Ho J, Coglianese E, Levy D, Colucci WS, Michael Felker G, Benjamin EJ, Januzzi JL, Wang TJ, Vasan RS. Association of novel biomarkers of cardiovascular stress with left ventricular hypertrophy and dysfunction: Implications for screening. *J Am Heart Assoc*. 2013; 2:e000399. [PubMed: 24200688]
24. Lind L, Wallentin L, Kempf T, Tapken H, Quint A, Lindahl B, Olofsson S, Venge P, Larsson A, Hulthe J, Elmgren A, Wollert KC. Growth-differentiation factor-15 is an independent marker of cardiovascular dysfunction and disease in the elderly: Results from the prospective investigation of the vasculature in uppsala seniors (pivus) study. *Eur Heart J*. 2009; 30:2346–2353. [PubMed: 19561023]
25. Pauriah M, Khan F, Lim TK, Elder DH, Godfrey V, Kennedy G, Belch JJ, Booth NA, Struthers AD, Lang CC. B-type natriuretic peptide is an independent predictor of endothelial function in man. *Clin Sci (Lond)*. 2012; 123:307–312. [PubMed: 22439818]
26. Okin PM, Gerds E, Kjeldsen SE, Julius S, Edelman JM, Dahlöf B, Devereux RB. Gender differences in regression of electrocardiographic left ventricular hypertrophy during antihypertensive therapy. *Hypertension*. 2008; 52:100–106. [PubMed: 18504323]
27. Flack JM, Gardin JM, Yunis C, Liu K. Static and pulsatile blood pressure correlates of left ventricular structure and function in black and white young adults: The cardia study. *Am Heart J*. 1999; 138:856–864. [PubMed: 10539816]
28. Lorber R, Gidding SS, Daviglius ML, Colangelo LA, Liu K, Gardin JM. Influence of systolic blood pressure and body mass index on left ventricular structure in healthy african-american and white young adults: The cardia study. *J Am Coll Cardiol*. 2003; 41:955–960. [PubMed: 12651040]
29. Arnett DK, Rautaharju P, Crow R, Folsom AR, Ekelund LG, Hutchinson R, Tyroler HA, Heiss G. Black-white differences in electrocardiographic left ventricular mass and its association with blood pressure (the ARIC study). *Atherosclerosis risk in communities*. *Am J Cardiol*. 1994; 74:247–252. [PubMed: 8037129]
30. Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS. Natural history of asymptomatic left ventricular systolic dysfunction in the community. *Circulation*. 2003; 108:977–982. [PubMed: 12912813]
31. Kuznetsova T, Herbots L, Jin Y, Stolarz-Skrzypek K, Staessen JA. Systolic and diastolic left ventricular dysfunction: From risk factors to overt heart failure. *Expert Rev Cardiovasc Ther*. 2010; 8:251–258. [PubMed: 20136611]
32. Fischer M, Baessler A, Hense HW, Hengstenberg C, Muscholl M, Holmer S, Doring A, Broeckel U, Riegger G, Schunkert H. Prevalence of left ventricular diastolic dysfunction in the community. Results from a doppler echocardiographic-based survey of a population sample. *Eur Heart J*. 2003; 24:320–328. [PubMed: 12581679]
33. Kuznetsova T, Herbots L, Lopez B, Jin Y, Richart T, Thijs L, Gonzalez A, Herregods MC, Fagard RH, Diez J, Staessen JA. Prevalence of left ventricular diastolic dysfunction in a general population. *Circ Heart Fail*. 2009; 2:105–112. [PubMed: 19808325]
34. Fernandes VR, Polak JF, Cheng S, Rosen BD, Carvalho B, Nasir K, McClelland R, Hundley G, Pearson G, O'Leary DH, Bluemke DA, Lima JA. Arterial stiffness is associated with regional ventricular systolic and diastolic dysfunction: The Multi-Ethnic Study of Atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2008; 28:194–201. [PubMed: 17962621]
35. Redfield MM, Jacobsen SJ, Borlaug BA, Rodeheffer RJ, Kass DA. Age- and gender-related ventricular-vascular stiffening: A community-based study. *Circulation*. 2005; 112:2254–2262. [PubMed: 16203909]
36. Borlaug BA, Kass DA. Ventricular-vascular interaction in heart failure. *Cardiol Clin*. 2011; 29:447–459. [PubMed: 21803232]

37. Rosen BD, Saad MF, Shea S, Nasir K, Edvardsen T, Burke G, Jerosch-Herold M, Arnett DK, Lai S, Bluemke DA, Lima JA. Hypertension and smoking are associated with reduced regional left ventricular function in asymptomatic: Individuals the Multi-Ethnic Study of Atherosclerosis. *J Am Coll Cardiol*. 2006; 47:1150–1158. [PubMed: 16545644]
38. Cheng S, Larson MG, McCabe EL, Osypiuk E, Lehman BT, Stanchev P, Aragam J, Benjamin EJ, Solomon SD, Vasan RS. Age- and sex-based reference limits and clinical correlates of myocardial strain and synchrony: The Framingham Heart Study. *Circ Cardiovasc Imaging*. 2013; 6:692–699. [PubMed: 23917618]
39. Rosen BD, Edvardsen T, Lai S, Castillo E, Pan L, Jerosch-Herold M, Sinha S, Kronmal R, Arnett D, Crouse JR 3rd, Heckbert SR, Bluemke DA, Lima JA. Left ventricular concentric remodeling is associated with decreased global and regional systolic function: The Multi-Ethnic Study of Atherosclerosis. *Circulation*. 2005; 112:984–991. [PubMed: 16103253]
40. Rosen BD, Fernandes VR, Nasir K, Helle-Valle T, Jerosch-Herold M, Bluemke DA, Lima JA. Age, increased left ventricular mass, and lower regional myocardial perfusion are related to greater extent of myocardial dyssynchrony in asymptomatic individuals: The multi-ethnic study of atherosclerosis. *Circulation*. 2009; 120:859–866. [PubMed: 19704101]
41. Kannel WB, Wolf PA. Framingham Study insights on the hazards of elevated blood pressure. *JAMA*. 2008; 300:2545–2547. [PubMed: 19050198]
42. Lloyd-Jones DM, Evans JC, Levy D. Hypertension in adults across the age spectrum: Current outcomes and control in the community. *JAMA*. 2005; 294:466–472. [PubMed: 16046653]
43. Frost PH, Davis BR, Burlando AJ, Curb JD, Guthrie GP, Isaacsohn JL, Wassertheil-Smoller S, Wilson AC, Stamler J. Coronary heart disease risk factors in men and women aged 60 years and older: Findings from the systolic hypertension in the elderly program. *Circulation*. 1996; 94:26–34. [PubMed: 8964114]
44. Lowe LP, Greenland P, Ruth KJ, Dyer AR, Stamler R, Stamler J. Impact of major cardiovascular disease risk factors, particularly in combination, on 22-year mortality in women and men. *Arch Intern Med*. 1998; 158:2007–2014. [PubMed: 9778200]
45. Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetiere P, Jousilahti P, Keil U, Njolstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM. Estimation of ten-year risk of fatal cardiovascular disease in europe: The score project. *Eur Heart J*. 2003; 24:987–1003. [PubMed: 12788299]
46. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, Abbott R, Godwin J, Dyer A, Stamler J. Blood pressure, stroke, and coronary heart disease. Part 1, prolonged differences in blood pressure: Prospective observational studies corrected for the regression dilution bias. *Lancet*. 1990; 335:765–774. [PubMed: 1969518]
47. O'Donnell CJ, Ridker PM, Glynn RJ, Berger K, Ajani U, Manson JE, Hennekens CH. Hypertension and borderline isolated systolic hypertension increase risks of cardiovascular disease and mortality in male physicians. *Circulation*. 1997; 95:1132–1137. [PubMed: 9054841]
48. Miura K, Daviglius ML, Dyer AR, Liu K, Garside DB, Stamler J, Greenland P. Relationship of blood pressure to 25-year mortality due to coronary heart disease, cardiovascular diseases, and all causes in young adult men: The chicago heart association detection project in industry. *Arch Intern Med*. 2001; 161:1501–1508. [PubMed: 11427097]
49. Kannel WB. Blood pressure as a cardiovascular risk factor: Prevention and treatment. *JAMA*. 1996; 275:1571–1576. [PubMed: 8622248]
50. Stokes J 3rd, Kannel WB, Wolf PA, D'Agostino RB, Cupples LA. Blood pressure as a risk factor for cardiovascular disease. The Framingham Study--30 years of follow-up. *Hypertension*. 1989; 13:113–118. [PubMed: 2535213]
51. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002; 360:1903–1913. [PubMed: 12493255]
52. Franklin SS, Larson MG, Khan SA, Wong ND, Leip EP, Kannel WB, Levy D. Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. *Circulation*. 2001; 103:1245–1249. [PubMed: 11238268]

53. Lloyd-Jones DM, Leip EP, Larson MG, Vasan RS, Levy D. Novel approach to examining first cardiovascular events after hypertension onset. *Hypertension*. 2005; 45:39–45. [PubMed: 15545512]
54. Cheng S, Gupta DK, Claggett B, Sharrett AR, Shah AM, Skali H, Takeuchi M, Ni H, Solomon SD. Differential influence of distinct components of increased blood pressure on cardiovascular outcomes: From the atherosclerosis risk in communities study. *Hypertension*. 2013; 62:492–498. [PubMed: 23876475]
55. Escobar E. Hypertension and coronary heart disease. *J Hum Hypertens*. 2002; 16(Suppl 1):S61–63. [PubMed: 11986897]
56. Taddei S, Salvetti A. Pathogenetic factors in hypertension. Endothelial factors. *Clin Exp Hypertens*. 1996; 18:323–335. [PubMed: 8743024]
57. Versari D, Daghini E, Virdis A, Ghiadoni L, Taddei S. Endothelium-dependent contractions and endothelial dysfunction in human hypertension. *Br J Pharmacol*. 2009; 157:527–536. [PubMed: 19630832]
58. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: Meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ*. 2009; 338:b1665. [PubMed: 19454737]
59. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *JAMA*. 1996; 275:1557–1562. [PubMed: 8622246]
60. Richards AM, Nicholls MG, Troughton RW, Lainchbury JG, Elliott J, Frampton C, Espiner EA, Crozier IG, Yandle TG, Turner J. Antecedent hypertension and heart failure after myocardial infarction. *J Am Coll Cardiol*. 2002; 39:1182–1188. [PubMed: 11923044]
61. Lee DS, Gona P, Vasan RS, Larson MG, Benjamin EJ, Wang TJ, Tu JV, Levy D. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: Insights from the framingham heart study of the national heart, lung, and blood institute. *Circulation*. 2009; 119:3070–3077. [PubMed: 19506115]
62. Ho JE, Gona P, Pencina MJ, Tu JV, Austin PC, Vasan RS, Kannel WB, D'Agostino RB, Lee DS, Levy D. Discriminating clinical features of heart failure with preserved vs. Reduced ejection fraction in the community. *Eur Heart J*. 2012; 33:1734–1741. [PubMed: 22507977]
63. Lee DS, Massaro JM, Wang TJ, Kannel WB, Benjamin EJ, Kenchaiah S, Levy D, D'Agostino RB Sr. Vasan RS. Antecedent blood pressure, body mass index, and the risk of incident heart failure in later life. *Hypertension*. 2007; 50:869–876. [PubMed: 17893376]
64. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ, Levy D. Lifetime risk for developing congestive heart failure: The Framingham Heart Study. *Circulation*. 2002; 106:3068–3072. [PubMed: 12473553]
65. Ekundayo OJ, Allman RM, Sanders PW, Aban I, Love TE, Arnett D, Ahmed A. Isolated systolic hypertension and incident heart failure in older adults: A propensity-matched study. *Hypertension*. 2009; 53:458–465. [PubMed: 19188527]
66. Butler J, Kalogeropoulos AP, Georgiopoulou VV, Bibbins-Domingo K, Najjar SS, Sutton-Tyrrell KC, Harris TB, Kritchevsky SB, Lloyd-Jones DM, Newman AB, Psaty BM. Systolic blood pressure and incident heart failure in the elderly. The cardiovascular health study and the health, ageing and body composition study. *Heart*. 2011; 97:1304–1311. [PubMed: 21636845]
67. Haider AW, Larson MG, Franklin SS, Levy D. Systolic blood pressure, diastolic blood pressure, and pulse pressure as predictors of risk for congestive heart failure in the Framingham Heart Study. *Ann Intern Med*. 2003; 138:10–16. [PubMed: 12513039]
68. Kass DA. Age-related changes in ventricular-arterial coupling: Pathophysiologic implications. *Heart Fail Rev*. 2002; 7:51–62. [PubMed: 11790922]
69. Chae CU, Pfeffer MA, Glynn RJ, Mitchell GF, Taylor JO, Hennekens CH. Increased pulse pressure and risk of heart failure in the elderly. *JAMA*. 1999; 281:634–639. [PubMed: 10029125]
70. Kane GC, Karon BL, Mahoney DW, Redfield MM, Roger VL, Burnett JC Jr. Jacobsen SJ, Rodeheffer RJ. Progression of left ventricular diastolic dysfunction and risk of heart failure. *JAMA*. 2011; 306:856–863. [PubMed: 21862747]

71. de Simone G, Gottdiener JS, Chinali M, Maurer MS. Left ventricular mass predicts heart failure not related to previous myocardial infarction: The cardiovascular health study. *Eur Heart J*. 2008; 29:741–747. [PubMed: 18204091]
72. Gradman AH, Alfayoumi F. From left ventricular hypertrophy to congestive heart failure: Management of hypertensive heart disease. *Prog Cardiovasc Dis*. 2006; 48:326–341. [PubMed: 16627048]
73. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB Sr. Newton-Cheh C, Yamamoto JF, Magnani JW, Tadros TM, Kannel WB, Wang TJ, Ellinor PT, Wolf PA, Vasan RS, Benjamin EJ. Development of a risk score for atrial fibrillation (Framingham Heart Study): A community-based cohort study. *Lancet*. 2009; 373:739–745. [PubMed: 19249635]
74. Healey JS, Connolly SJ. Atrial fibrillation: Hypertension as a causative agent, risk factor for complications, and potential therapeutic target. *Am J Cardiol*. 2003; 91:9G–14G.
75. Mitchell GF, Vasan RS, Keyes MJ, Parise H, Wang TJ, Larson MG, D'Agostino RB Sr. Kannel WB, Levy D, Benjamin EJ. Pulse pressure and risk of new-onset atrial fibrillation. *JAMA*. 2007; 297:709–715. [PubMed: 17312290]
76. Go O, Rosendorff C. Hypertension and atrial fibrillation. *Curr Cardiol Rep*. 2009; 11:430–435. [PubMed: 19863867]
77. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA*. 1994; 271:840–844. [PubMed: 8114238]
78. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, White R, Furberg CD, Rautaharju PM. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation*. 1997; 96:2455–2461. [PubMed: 9337224]
79. Thomas MC, Dublin S, Kaplan RC, Glazer NL, Lumley T, Longstreth WT Jr. Smith NL, Psaty BM, Siscovick DS, Heckbert SR. Blood pressure control and risk of incident atrial fibrillation. *Am J Hypertens*. 2008; 21:1111–1116. [PubMed: 18756257]
80. Milan A, Caserta MA, Dematteis A, Naso D, Pertusio A, Magnino C, Puglisi E, Rabbia F, Pandian NG, Mulatero P, Veglio F. Blood pressure levels, left ventricular mass and function are correlated with left atrial volume in mild to moderate hypertensive patients. *J Hum Hypertens*. 2009; 23:743–750. [PubMed: 19262581]

Abbreviations: ANP = atrial natriuretic peptide, ACE = angiotensin converting enzyme, ATII = angiotensin II, B2BK2 = bradykinin 2 receptor, BNP = brain natriuretic peptide, CAD = coronary artery disease, CRP = C-reactive protein, HFPEF = heart failure with preserved ejection fraction, LA = left atrium, LVH = left ventricular hypertrophy, PAI-1 = plasminogen activator inhibitor-1, sGC = soluble guanylate cyclase.

Figure 1. Pathogenesis of hypertensive cardiac disease

The pathogenesis of hypertension and several common cardiac conditions share genetic, biologic, and clinical determinants. Independently, and through hypertension, these common risk factors are associated with the initial development of subclinical alterations in cardiac structure and function as well as the eventual development of overt clinical cardiac disease. To illustrate this concept, examples are highlighted for three outcomes: atrial fibrillation (green), heart failure with preserved ejection fraction (red), and atherosclerotic coronary artery disease (purple). Note that these examples are only illustrative and not exhaustive, as the spectrum of mechanistic common ground is broad and multifactorial.