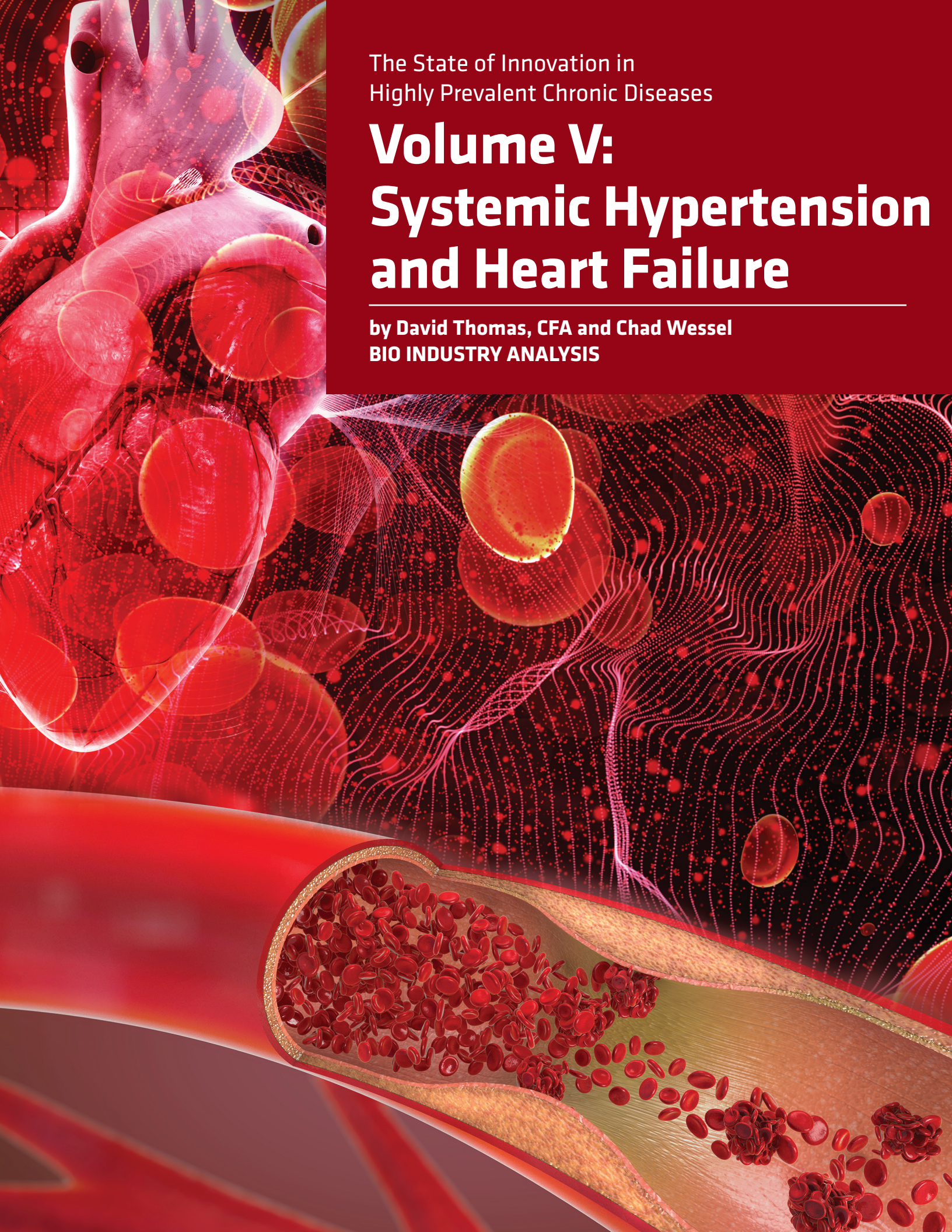

The State of Innovation in
Highly Prevalent Chronic Diseases

Volume V: Systemic Hypertension and Heart Failure

by David Thomas, CFA and Chad Wessel
BIO INDUSTRY ANALYSIS

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Introduction

This is the fifth report in a series on the innovation landscape of highly prevalent, chronic diseases. In our previously published research, emerging company investment for drug development in many common diseases was shown to be declining and low relative to total healthcare costs (**Figure 1**). This prompted the ongoing investigation to determine if the slowdown is industry-wide, beyond privately funded companies. Thus far, we have identified a broader contraction of R&D in depression, pain, addiction, type II diabetes, and obesity.[1] We have also seen limited growth in the net number of clinical pipeline programs for chronic indications (**Figure 3**).

The cause for concern is magnified by the impact these chronic disease areas have on the overall healthcare system in the U.S. For example, for treating cardiovascular disease in the U.S., the American Heart Association estimates current direct costs at $277 billion annually and expects costs to grow to $655 billion by 2035.[2] Although these current and projected costs for cardiovascular disease are staggering, venture capital investment for cardiovascular-focused therapeutic companies in the U.S. remains 13 times lower than oncology-focused companies (**Figure 2**). Combined with recent exits out of cardiovascular disease by larger pharmaceutical companies and stagnating growth in the clinical pipeline, these low venture funding levels suggest there may be fewer innovative solutions in the future. Low clinical success rates seen in cardiovascular disease drug development (**Figure 4**) suggest more investment is needed across diverse therapeutic strategies, rather than below average investment in a narrow set of strategies or investment solely focused on reformulations and previously identified targets.

This volume takes an in depth look at the state of innovation for therapeutics in two major cardiovascular disease indications, systemic hypertension and heart failure. Hypertension and heart failure, combined, cost the U.S. healthcare system $86 billion annually and affect over 100 million Americans.[3] Herein, we assess the depth and breadth of current therapeutic options and the innovation progressing through the clinical pipeline targeting the urgent needs of patients suffering from cardiovascular disease.

1 Thomas, D., Wessel, C. BIO Industry Analysis. Highly Prevalent Chronic Disease Series, (2018) (www.bio.org/iareports)
2 Cardiovascular disease: A Costly Burden for America, Projections Through 2035, pg.10 (total costs above do not include stroke and are specific for hypertension and heart failure)
3 Cardiovascular disease: A Costly Burden for America, Projections Through 2035, pg.3

U.S. HEALTHCARE COST VS. U.S. VENTURE CAPITAL FUNDING OF NOVEL R&D FOR HIGHLY PREVALENT CHRONIC DISEASES

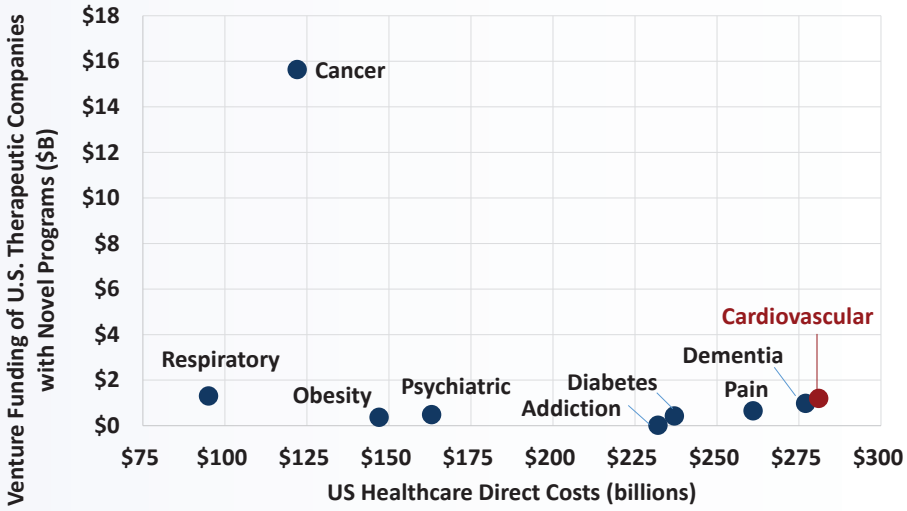


Figure 1. Healthcare Cost vs. Venture Capital Funding into novel chemical entity development 2008-2018 for Oncology and highly prevalent chronic diseases. Source for healthcare costs – Cardiovascular disease: AHA 2017 Direct costs excluding stroke, Cardiovascular disease: A Costly Burden for America, Projections Through 2035, pg.10; Dementia: Alzheimer's Association, 2018. Diabetes: ADA report, March 2018; Obesity, Heart Disease, Respiratory, Oncology are based on 2013 data cited in Health Affairs, 35, No. 6 (2016); Pain: The Journal of Pain, 2012; Addiction: NIDA website 2018. Source for venture data: BIO Industry Analysis, Emerging Company Trend Report, 2009-2018 (accessed in June 2019 at www.bio.org/ia-reports).

2009-2018 VENTURE INVESTMENT INTO U.S. COMPANIES WITH LEAD NOVEL DRUG PROGRAMS IN ONCOLOGY VS. CARDIOVASCULAR DISEASE

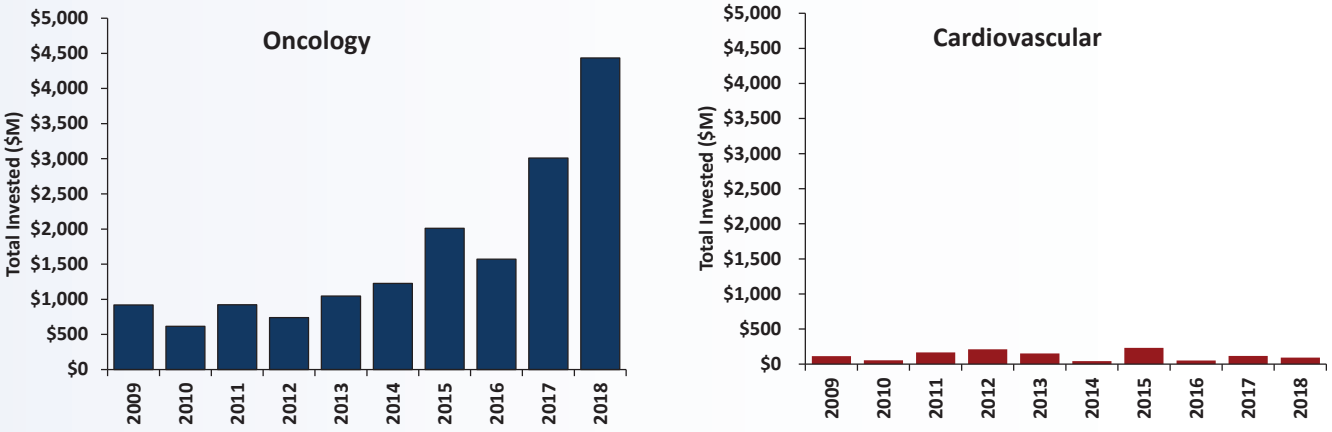


Figure 2. Left: Venture funding of companies with lead products in oncology, 2009-2018. Right: Venture funding of companies with lead products in cardiovascular disease, 2009-2018. Venture investment into oncology is 13 times more than the funding received for novel cardiovascular drugs during this time period. Only four companies with lead cardiovascular disease drugs were financed each year on average. By comparison, there were 80 oncology companies financed each year, on average, suggesting that early-stage investors currently prioritize oncology over cardiovascular disease.

CLINICAL PIPLEINE GROWTH 2015 VS 2019

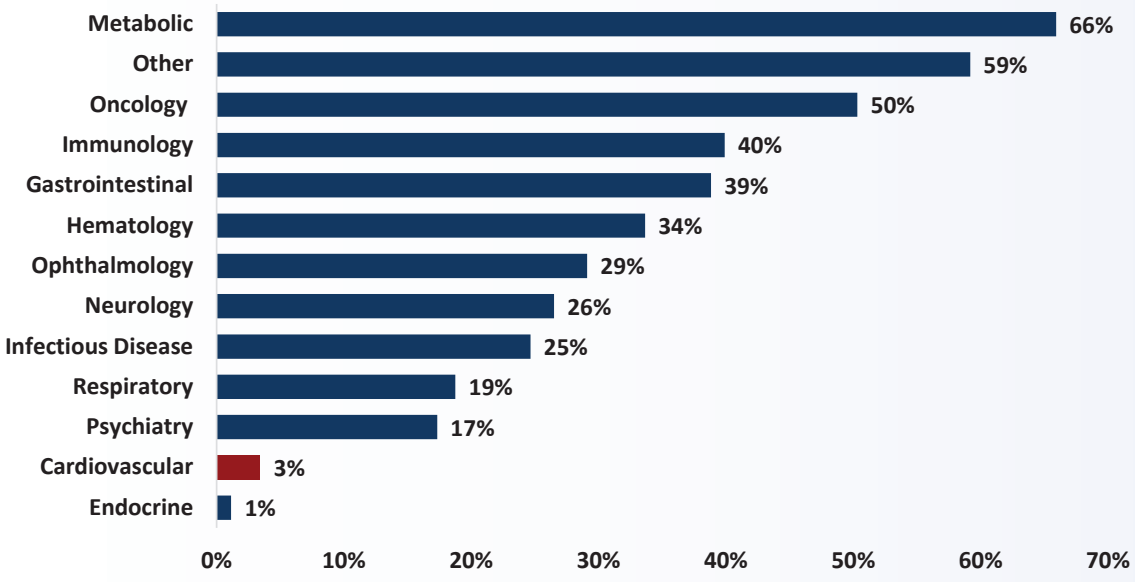


Figure 3. Net growth of the clinical pipeline by disease area, 2015 vs. 2019. Cardiovascular has only grown by 3% over four years, whereas the metabolic area, with numerous rare disease programs, has grown by 66%. Source data: BIO Industry Analysis, Emerging Company Trend Report, 2015 and 2019 reports (accessed in June 2019 at www.bio.org/ia-reports).

CLINICAL DEVELOPMENT SUCCESS RATES FOR NOVEL CARDIOVASCULAR DISEASE DRUGS 2008-2019

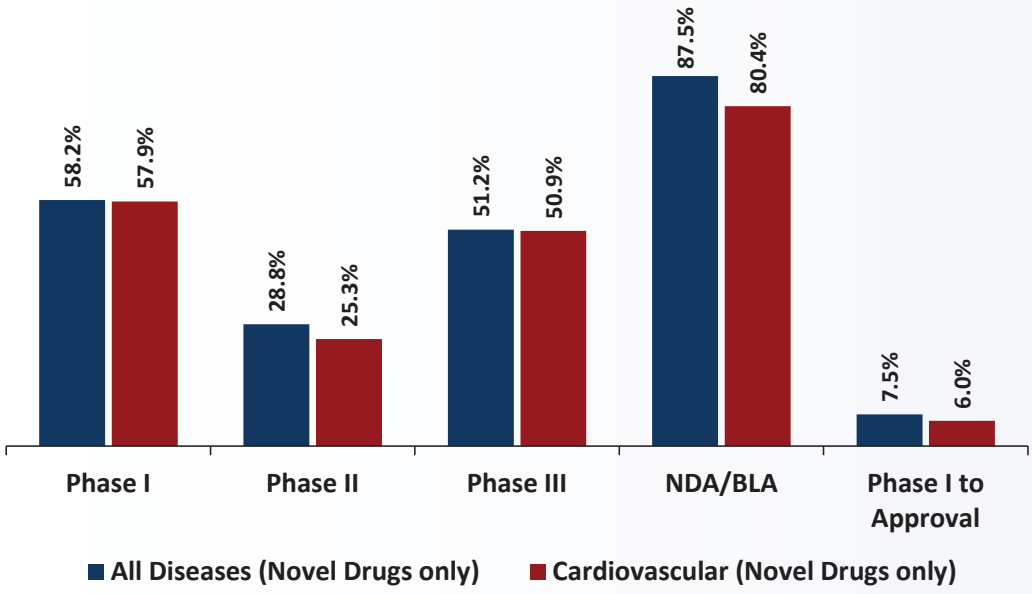


Figure 4. Clinical success rates for novel drug programs across all cardiovascular disease indications compared to success rates for all disease areas combined, January 2008 through January 2019. Data is based on drug program transitions listed in the Informa Biomedtracker and Pharmapremia databases. The clinical trial success rates for novel cardiovascular disease drug candidates were found to be slightly lower than what is observed across all disease area clinical programs. Cardiovascular drug development programs in Phase II had a 25.3% chance of transitioning to Phase III vs. 28.8% across all diseases. Approval of filed NDA or BLAs for cardiovascular had only an 80.4% success rate vs. 87.5% across all diseases.

Key Takeaways for Systemic Hypertension Therapeutics

- **Marketed drugs**: There are currently 68 FDA-approved new chemical entities (NCEs) for treating hypertension. These drugs use three physiological strategies (vasodilation, heart rate reduction, and diuresis) across 14 molecular targets. Only one new drug class has been approved over the last 20 years.
- **Pipeline**: There are 18 clinical-stage drug programs for treating hypertension. However, only six of these programs involve new molecular targets. A total of five new targets are being investigated in the clinic. The majority of drug programs are for mechanisms of action targeted by therapies that are already approved, and there is only one Phase III program for a new target in systemic hypertension.
- **Clinical trial initiations**: Phase I trial initiations have declined over the last decade, with 16 trials from 2009-2014 vs seven in the period 2012-2018. Phase II trial starts do not show a detectable trend, with only one to three trial initiations per year. Phase III trial starts have ranged from no trial starts to only one or two depending upon the year.

Key Takeaways for Heart Failure Therapeutics

- **Marketed drugs**: There are currently 31 FDA-approved new chemical entities (NCEs) for treating congestive heart failure. The majority (87%) of these FDA-approved NCEs are also approved for systemic hypertension. Marketed heart failure drugs use the same three physiological strategies as hypertension (vasodilation, heart rate reduction, and diuresis). However, of the 12 molecular targets for the heart failure NCEs, three are unique to heart failure and not approved for hypertension. Two of these unique molecular targets had NCE approvals in the last decade, signifying recent innovation in this field.
- **Pipeline**: There are 28 clinical-stage drug programs for treating heart failure, with 23 of these programs involving NCEs across 14 new molecular targets. There are three times as many novel programs in heart failure than hypertension.
- **Clinical trial initiations**: Phase II trial starts have increased substantially from a low of two in 2009 to eight in 2018, suggesting an increased focus on innovative R&D. However, Phase III trial starts have remained at two or less per year over the last decade.

Current Therapies for Systemic Hypertension and Heart Failure

Systemic hypertension is a contributing factor to coronary artery disease (CAD), stroke, kidney disease, and heart failure. Hypertension directly affects some 96.1 million people in the U.S. alone and contributes to the prevalence of the 16.8 million people with CAD, 7.5 million with stroke, and 5.8 million with heart failure.[4] Systemic hypertension is defined as high blood pressure in the vessels carrying blood to the body's organs, with the exception of the lungs. The link between hypertension and heart failure has been studied extensively over the last few decades. According to one longitudinal study, hypertension was present in 91% of individuals that went on to develop heart failure.[5] Heart failure occurs when the heart has trouble pumping blood out of the heart to the rest of the body and can be exacerbated by high blood pressure. In addition to hypertension, heart failure can also be caused by prior heart attack, valvular diseases, or other diseases of the heart muscles. Congestive heart failure refers to the buildup of blood fluid in the heart due to either poor ejection from the heart or poor relaxation of heart muscles and thus filling of the heart.

Obesity, diabetes, kidney disease, and hyperlipidemia can all contribute to hypertension and exacerbate heart failure. As poor diet, smoking, and lack of exercise are main contributors to those diseases, a first recommendation by physicians is to correct lifestyle practices. However, in many cases, lifestyle changes cannot reverse the progression of the disease and physicians rely on medication to intervene.

The first drugs for hypertension and heart failure were initially developed in the 1950s. However, some classes that were approved and indicated for hypertension did not receive FDA approval for the heart failure indication until decades later when enough clinical data was compiled showing a statistically significant benefit in heart failure patients. The rationale behind the dual indications is that hypertension drugs reduce the workload and stress of the failing heart.

In **Figure 5**, a timeline reveals the overlap in drug class approvals for the two inter-related indications. Marketed hypertension drugs work on 14 molecular targets and marketed drugs for heart failure work on 12 molecular targets. Of these 12 molecular targets for heart failure, seven overlap with hypertension. For NCEs, the overlap is 87%, as will be discussed in more detail below.

Figure 5 also illustrates the age of approved mechanistic drug classes for these two indications. More than 90% of hypertension NCEs and 70% of heart failure NCEs are now off-patent and the majority are available as generics. Most of the original innovation, by volume of new drugs approved, took place first in the 1950s and 1960s, then again in the 1980s. In fact, only three new drug classes have been approved over the last 20 years, each with a single NCE (one NCE for hypertension and two unique NCEs for heart failure).

[4] American Heart Association. Cardiovascular disease: A Costly Burden for America, Projections Through 2035, pg.3

[5] Messerli, F., et al. The Transition from Hypertension to Heart Failure. Contemporary Update (2017) and Levy, D., et.al., The progression from hypertension to congestive heart failure. JAMA. 275, 1557–1562 (1996).

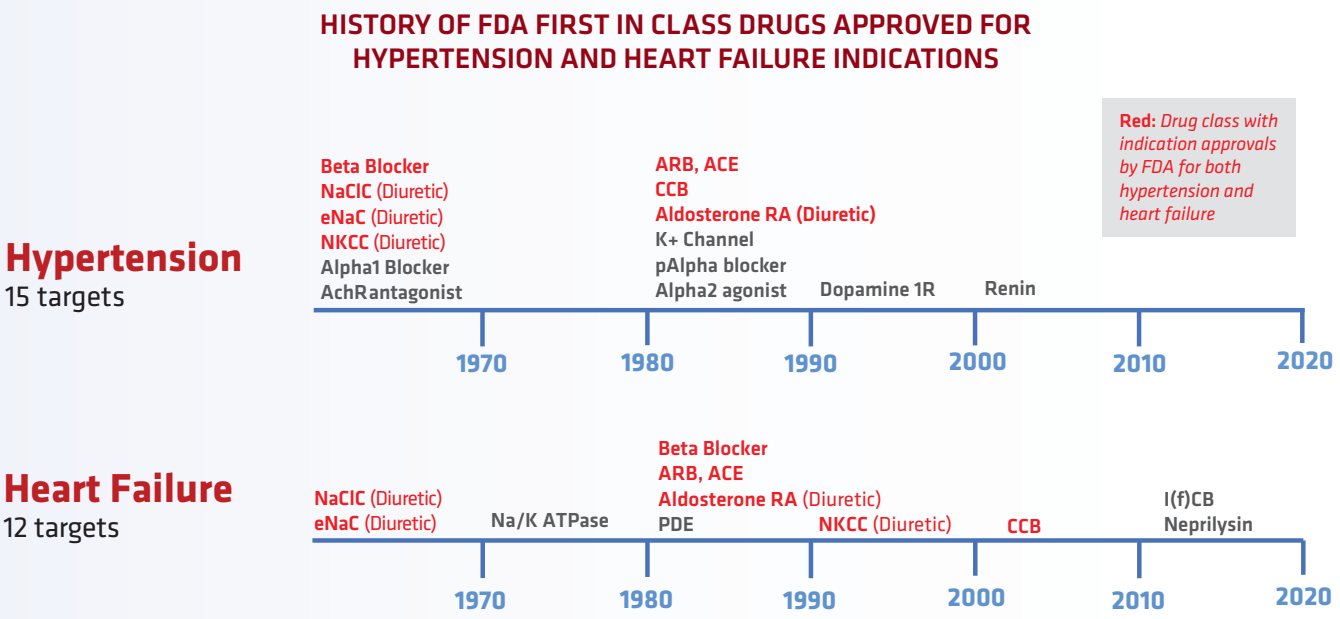


Figure 5. Timeline of first-in-class drug approvals by FDA for hypertension and heart failure, mapped to decade approved. The labels before 1970 extend to 1953 when the first hypertension and CHF drug were approved. Drug classes approved in both hypertension and heart failure are in red. Beta and Alpha blockers: adrenergic receptor antagonists; NaClC: sodium chloride cotransporter; eNaC: endothelial sodium channel; NKCC: sodium potassium cotransporter; Aldosterone RA: receptor antagonists. AchR: acetylcholine receptor, ARB: angiotensin receptor blocker, ACE: angiotensin converting enzyme, CCB: calcium channel blockers; K+: potassium, Dopamine 1R: dopamine receptor partial agonist; renin inhibitor (aliskirin, 2007); PDE: phosphodiesterase 3 and 4, Na/K ATPase: sodium/potassium ATPase inhibitor (digoxin, 1975), Neprilysin inhibitor (sacubitril in Entresto, 2015), I(f)CB: I(f) ion channel blocker (Ivabradine, 2015)

In **Figures 6** and **7**, a more comprehensive table of currently marketed NCEs in the U.S. is shown for hypertension and heart failure. Note that these tables include active ingredients themselves, and not "drugs" per se, to avoid duplicate counting for reformulated products. While there are 68 active NCEs approved for systemic hypertension (**Figure 6**), only 31 NCEs are approved for congestive heart failure (**Figure 7**). Of the 31 NCEs approved in heart failure, only five are not approved for hypertension as indicated in **Figure 7**.

As mentioned above, three physiological strategies are employed by the NCEs targeting hypertension and heart failure: 1) vasodilation of blood vessels to allow more blood flow with less pressure, 2) a diuretic effect to reduce blood volume and salt concentrations, and 3) reduction of heart rate. Each of the drug targeting mechanisms used within each physiological strategy will be described below in more detail.

FDA APPROVED NCES FOR CHRONIC, SYSTEMIC HYPERTENSION (N=68)

	Target/MOA	1st FDA Approval in hypertension	# Active NCEs (inactive)	Chemical Entity
vasodilation	Calcium channel blocker (CCBs) and Calcium flux inhibitors*	1953#, 1981	10	hydralazine#, amlodipine, nifedipine*, verapamil*, diltiazem*, nicardipine*, isradipine*, felodipine*, nisoldipine*, clevidipine*
	Alpha 1 adrenoceptor antagonist	1953	3 (1)	phenoxybenzamine*, prazosin*, doxazosin*
	nACh receptor antagonist	1956	1	mecamylamine* (for severe hypertension)
	ACE inhibitors	1981	10	captopril, enalapril, lisinopril, benazepril, fosinopril, quinapril, ramipril, trandolapril, perindoprilt*, moexipril*
	Angiotensin II receptor antagonist (ARBs)	1981	8 (1)	candesartan, valsartan, losartan*, irbesartan*, eprosartan*, telmisartan*, olmesartan*, azilsartan*
	Alpha 2 adrenoceptor agonist (centrally acting)	1982	4	guanabenz*, clonidine*, methyldopa*, guanfacine*, phentolamine*
	Potassium channel activator	1989	1	pinacidil*
	DOP1 receptor (D1) partial agonist	1997	1	fenoldopam*
	Renin inhibitor	2007	1	aliskiren*
heart rate	Beta adrenoceptor antagonist	1967	12 (3)	metoprolol, bisoprolol, carvedilol, propranolol*, nadolol*, atenolol*, pindolol*, acebutolol*, labetalol*, betaxolol*, carteolol*, nebivolol*
diuretic	Renal sodium chloride cotransporter (thiazides and analogues)	1959	10	chlorthalidone, metolazone, hydrochlorothiazide, indapamide, chlorothiazide*, bendroflumethiazide*, hydroflumethiazide*, methyclothiazide*
	Renal epithelial sodium channel (eNaC)	1964	2	triamterene, amiloride
	Renal sodium potassium cotransporter (NKCC)	1966	3	bumetanide, furosemide, torsemide
	Aldosterone receptor antagonist	1986	2	spironolactone, eplerenone

Figure 6. FDA approved new chemical entities (NCEs) for systemic hypertension, listed by physiologic strategy, then by target/mechanism of action, followed by year of first in class approval for the specific indication. Not shown in the table are drugs used in the acute setting. In 1974, nitroprusside was FDA approved for acute hypertension setting, and later in 1990, a second nitrate guanylate cyclase (nitroglycerin) was approved. Nitric oxide (NO) activates smooth muscle soluble guanylyl cyclase (GC) eventually decreasing muscle cell calcium contractions, leading to rapid smooth muscle relaxation. In 1998, a dual alpha 1,2 adrenoreceptor antagonist, was FDA approved for acute, not chronic hypertension. Discontinued drugs not shown: In 1955, reserpine (an inhibitor of norepinephrine and dopamine vesicle storage in neurons) was approved by the FDA but has since been discontinued. The alpha 1 agonist guanadrel was approved by the FDA in 1982 but has been discontinued.

*** NCEs not approved in heart failure.**

 # Hydralazine was approved in 1953, but all CCBs were approved after 1980 (hydralazine is not a direct CCB but is believed to work through calcium flux to reax smooth muscle and dilate blood vessels.

FDA APPROVED NCES FOR CONGESTIVE HEART FAILURE (N=31)

	Target/MOA	1st FDA Approval in CHF	# Active NCEs (inactive)	Chemical Entity
vasodilation	ACE inhibitor	1981	8	captopril, enalapril, lisinopril, benazepril, fosinopril, quinapril, ramipril, trandolapril
	Angiotensin II receptor antagonist (ARBs)	1981	2	candesartan, valsartan
	PDE inhibitors (PDE3, PDE4)	1984	2	milrinone*, inamrinone*
	Calcium channel blocker (CCB)	2005	2	amlodipine, hydralazine
	Neprilysin inhibitor	2015	1	sacubitril* (with valsartan)
heart rate	Na/K ATPase inhibitor	1975	1	digoxin*
	Beta adrenoceptor antagonist	1982	3	metoprolol, carvedilol, bisoprolol
	I(f) channel blocker (natural pacemaker current)	2015	1	ivabradine*
diuretic	Renal sodium chloride cotransporter (thiazides and analogues)	1958	4	chlorothiazide, metolazone, hydrochlorothiazide, indapamide
	Renal epithelial sodium channel (eNaC)	1964	2	triamterene, amiloride
	Renal sodium potassium cotransporter (NKCC)	1972	3	bumetanide, furosemide, torsemide
	Aldosterone antagonist	1986	2	spironolactone, eplerenone

Figure 7. FDA approved new chemical entities (NCEs) for congestive heart failure, listed by physiologic strategy, then by target/mechanism of action, followed by year of first of the class approval for the specific indication of heart failure. Not shown in table are drugs used only for the acute setting, such as acute decompensated HF (nesiritide recombinant, atrial natriuretic peptide receptor A, approved in 2001) and drugs for rare cardiomyopathies. Also excluded from the table are atorvastatin and other statins as they were approved for reduction in potential secondary cardiac events, such as MI, not for treating CHF directly. Bumetanide is listed as an NKCC (sodium potassium cotransporter) inhibitor but may have other mechanistic properties beyond NKCC. It is therefore the only NKCC approved in CHF (two other NKCC inhibitors, furosemide and torsemide, are approved for hypertension).

*** NCEs not approved in hypertension (all others have been approved for use in hypertension).**

Vasodilating Drugs on the Market

FDA approved vasodilating drugs work through nine different molecular targets. Seven of these targets are found in the hypertension arsenal, three of which are shared by the heart failure drugs. The vasodilating drug mechanisms that overlap both indications tend to be used as "first-line therapies": angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and calcium-channel blockers (CCBs).

In 1981, the first ACE inhibitors and ARBs were approved for marketing in the U.S. These work by inhibiting specific enzymatic activities within the renin-angiotensin-aldosterone system (RAAS), a well-established physiological pathway the body uses to regulate blood pressure, vasoconstriction, blood volume, and blood electrolyte balance (see diagram below). In fact, there are a total of four classes of drugs that work through the RAAS, two of which will be described under diuretic mechanisms. Multiple clinical-stage drug development programs also target different nodes along the RAAS.

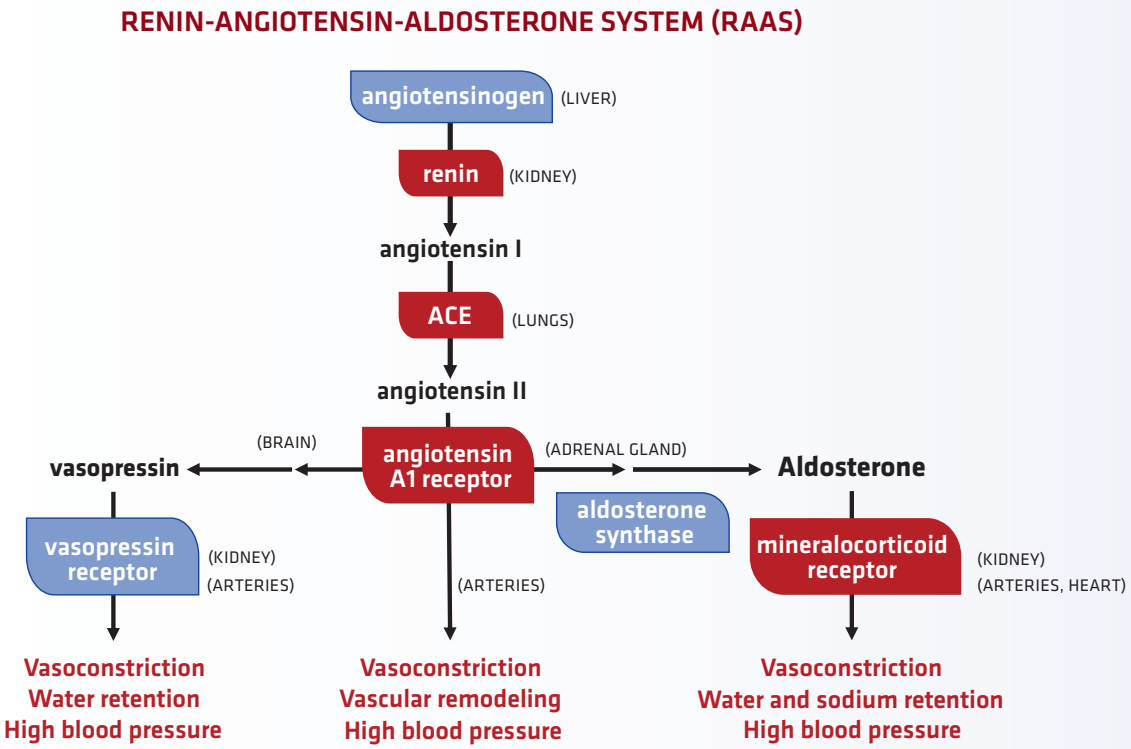


Diagram of the Renin-Angiotensin-Aldosterone System (RAAS) and vasopressin. Adapted from Braunwald's Heart Disease, Eleventh Edition (Elsevier, 2019), Medical Pharmacology and Therapeutics, Fourth Edition (Saunders, 2014), and https://www.cvphysiology.com. Red shaded boxes are for targets of FDA approved drugs for hypertension and/or heart failure. Blue boxes are for ongoing clinical-stage program targets in hypertension (angiotensinogen and aldosterone synthase) and heart failure (vasopressin receptor, downstream of the core RAAS components).

The bulk of RAAS regulation throughout the body is related to angiotensin II's activity. Angiotensin II, through its binding of receptors on various tissues and organs, can directly and indirectly increase blood pressure, fluid retention, and sodium levels. The indirect activation of this regulation occurs at two sites: 1) the adrenal gland, which leads to the production and release of aldosterone, a steroidal hormone, and 2) the pituitary gland in the brain, which influences the release of vasopressin, an anti-diuretic peptide hormone. Direct activation occurs through angiotensin II receptors on blood vessels themselves, which leads to contraction of smooth muscle cells.

For angiotensin II to be fully formed and activated within the blood, two enzymatic steps must occur in the blood. Blocking these steps form the basis of two drug intervention methods. First, a mature protein called renin must be secreted by the kidney and processed. This active renin protein then enzymatically processes a precursor called angiotensinogen to angiotensin I, which is then secreted by the liver. Finally, angiotensin I is converted to angiotensin II, by the aptly named angiotensin converting enzyme, or ACE. There are 10 ACE inhibitors on the market for hypertension and eight for heart failure. One renin inhibitor is approved, but only for hypertension.

Tangential to those enzymatic inhibition steps within RAAS are the angiotensin receptor blockers, or ARBs. The ARBs perform their function at the site of angiotensin II receptors, preventing the vasoconstricting process by blocking angiotensin II activity.

Calcium-channel blockers (CCBs) also arrived on the market in 1981. The CCBs target smooth muscle and cardiac tissue calcium channels by blocking the influx of calcium, which muscle cells rely on for contraction. The 1953 approval of hydralazine precedes the nine CCB approvals and is believed to act through a similar mechanism. For hydralazine, the exact calcium flux blocking mechanism is not understood completely, and thus is not technically referred to as a CCB.

The three first-line therapies for vasodilation described above (ACE inhibitors, ARBS, and CCBs) have the most NCEs approvals listed in **Figures 6** and **7**, with 28 approved for hypertension and 12 approved for heart failure. Almost all of these are now available as generics.

Two adrenoreceptor target mechanisms are approved for hypertension (**Figure 6**), but not in heart failure: alpha 1 adrenoceptors, located on the smooth muscle cells of blood vessels, and alpha 2 adrenoceptors found in the brain. Alpha 1 antagonists (alpha blockers) act to directly block the peripheral vasoconstricting effects of circulating epinephrine and norepinephrine released from neurons. Three have been approved for hypertension. The four FDA approved alpha 2 adrenoceptor agonists work in a more complex manner. Alpha 2 adrenoceptors serve the biological function of lowering norepinephrine signaling through a negative feedback loop at the site of neurons. Agonists activate this negative feedback loop and thus dampen norepinephrine's ability to activate the sympathetic stress response, which includes vasoconstriction.[6]

The remaining vasodilating mechanisms have a single NCE approval each. Three of these are for hypertension alone: a nicotinic acetylcholine (nACh) receptor antagonist, potassium channel activator, and a dopamine 1 receptor agonist. The nicotinic acetylcholine (nACh) receptor antagonist, mecaylamine, works by reversing the constriction effects of acetylcholine. This can be thought of as the opposite of nicotine's activity, which stimulates nACh receptors and constricts blood vessels. Activation of potassium channels, the target of pinacidil, leads to direct relaxation of vascular smooth muscles and dilation. A centrally acting drug, fenoldopam, works through peripheral dopamine receptors to decrease blood pressure.

The final two vasodilation targets are used by heart failure drugs, but not hypertension drugs: Phosphodiesterase (PDE) and neprilysin. Phosphodiesterases are known to limit the amount of cyclic nucleotides signaling molecules, cAMP and/or cGMP, within muscle cells. Blocking PDE3 or PDE4 specifically leads to an increase in cAMP, which acts as a secondary messenger for increased calcium influx in vascular smooth muscle cells. This calcium influx, as noted above with CCBs, induces relaxation of blood vessels. The neprilysin inhibitor sacubitril is approved as a combination drug (Entresto) with valsartan, an ARB. Inhibition of neprilysin prevents the degradation of natriuretic peptides. The build of natriuretic peptides leads to higher activity of their vasodilating properties.

Heart Rate Lowering Drugs on the Market

For hypertension, beta adrenoceptor antagonist (beta blockers), are the only class of drugs that primarily function by lowering heart rate (**Figure 6)**. They also have vasodilating effects in peripheral vasculature, but their effect on beta receptors expressed in heart tissue sets them apart from the alpha adrenoreceptor class mentioned above. A total of 12 NCEs are marketed for hypertension and are classified as beta blockers. This is not the case for heart failure where all adrenoreceptor antagonists were once contraindicated. In 1982, that changed with the first approval of a beta adrenoceptor antagonist in heart failure. Clinical studies showed that beta blockers, introduced slowly in patients with stable heart failure with reserved ejection fraction (HFrEF), significantly increased survival. Beta blockers reduce the workload on the heart, hypertrophy, fibrosis, and myocyte apoptosis, and restore excitation-contraction coupling.[7] There are currently three beta blocker NCEs approved for heart failure **(Figure 7)**.

Two unique target mechanisms for heart failure (not approved for hypertension) can be found in **Figure 7**. Each has a single NCE approval: the Na/K ATPase inhibitor digoxin, approved back in 1975, and the more recently approved I(f) channel blocker Ivabradine. Digoxin works by inhibiting sodium export in heart muscle. This in turn leads to calcium retention which is responsible for increased heart contraction. Ivabradine works as an inhibitor of the natural pacemaker current in the heart.

[6] Giovannitti, J., et al. Alpha-2 Adrenergic Receptor Agonists: A Review of Current Clinical Applications. Anesth Progress. 62 (1), 31–38 (2015)
[7] Medical Pharmacology and Therapeutics, Fourth Edition (Saunders, 2014)

Diuretic Drugs on the Market

As the kidney is responsible for filtering salts and retaining water in the blood, most diuretics work at the site of this organ. By increasing sodium release, diuretic drugs also increase the release of water in the urine. Decreased blood volume results in lower overall blood pressure. In heart failure less blood is often found flowing through the kidneys. This decreased renal flow can result in increased RAAS response and more fluid buildup throughout the body. For example, the lungs can also be affected by high blood volume leading to pulmonary edema. Various drugs have been developed to address these occurrences.

The drugs that target renal sodium chloride cotransporter (by thiazides and analogues) and sodium potassium cotransporter (NKCC, loop diuretics) work by a process of diuresis (water loss) and natriuresis (lowering sodium). They block the reabsorption of sodium and allow for more water to be excreted in the urine. However, they can cause potassium loss. Two other classes of diuretics do not lead to potassium loss. Many of these "potassium sparing" drugs can be used with the thiazide or loop diuretics to prevent potassium loss.

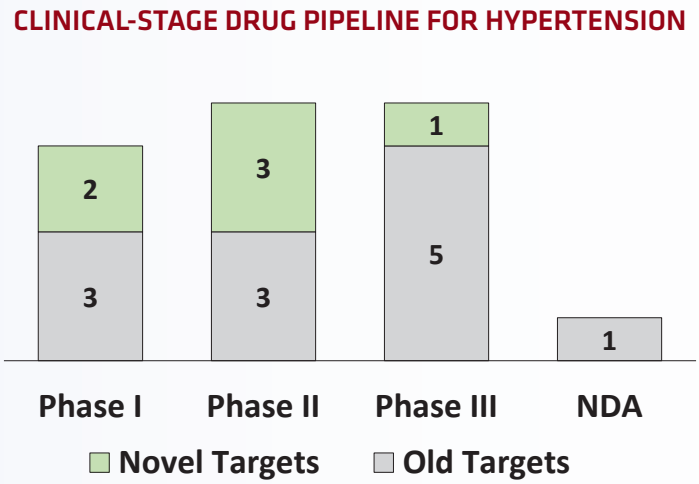
The first "potassium sparing" diuretics to be approved were the epithelial sodium channel (eNaC) inhibitors. Although they have a weaker ability to reverse salt and water reabsorption than the thiazides and loop diuretics above, they have the benefit of less potassium passing into the urine.

Aldosterone receptor antagonists, the second group of "potassium sparing" diuretics, block and reverse the antidiuretic effects of aldosterone (mentioned above in the RAAS description). The two drugs in this class are approved for both hypertension and heart failure. As with most hypertension drugs, they are available as generics.

Clinical Pipeline in Systemic Hypertension

Despite availability of generic antihypertensive agents, there remains unmet need for patients that experience side effects or are treatment-resistant to current therapies. More than a dozen companies are developing the next generation of drugs to meet these needs.

The total clinical pipeline for systemic hypertension consists of 18 drug programs with six of these involving novel targets. In **Figure 8**, the 18 clinical programs are shown by Phase of development and the six new targets are organized by mechanism of action. For Phase III programs, there is one NCE program for a novel target and five NCE programs for older targets. All but one of the novel programs in hypertension work via a vasodilation strategy.



Hypothesis - target	Phase I	Phase II	Phase III	NDA
endothelin receptors	0	0	1	0
angiotensinogen	1	1	0	0
aminopeptidase A	0	1	0	0
ammonia oxidizing bacteria	0	1	0	0
aldosterone synthase	1	0	0	0
Total	2	3	1	0

Figure 8. The clinical pipeline for systemic hypertension by Phase (as of September 2019), based on Biomedtracker's classification methodology by Phase of development as well as company website information. Programs listed as "Ex-U.S." in the Biomedtracker database are included here by Phase based on independent research of company websites. This "Ex-U.S." listing implies the companies have not yet intended to seek FDA approval. Right: The number of programs in each of the target strategies by clinical Phase.

Two angiotensinogen RNA targeting dugs are in development. One is an antisense drug in Phase II and the other is an RNAi drug in Phase I. These two strategies work by interfering upstream of the ACE inhibitor and renin drugs to control the production of the parent protein in the RAAS, angiotensinogen.

A Phase II aminopeptidase A inhibitor is being developed to target the brain's RAAS. Within the brain, angiotensin II can be further converted to angiotensin III by aminopeptidase A. Angiotensin III has been shown to regulate arterial tone and preclinical studies suggest targeting brain aminopeptidase A may attenuate sympathetic hyperactivity and cardiac dysfunction after a heart attack.

A dual endothelin (ETa and ETb) receptor antagonist prodrug is in Phase III. The active metabolites bind to both endothelin ETa and ETb receptors blocking endothelin-1 causing vasodilation. The metabolite of the prodrug is approved in pulmonary artery hypertension.

The fifth program in clinical development for hypertension is a single strain of beneficial ammonia oxidizing bacteria delivered intranasally. The bacteria are capable of converting ammonia to nitric oxide, thus aiming to induce vasodilation.

Lastly, one diuretic is found in the systemic hypertension pipeline. Like the approved aldosterone/ mineralocorticoid receptor antagonists, it acts through the RAAS regulating fluid and electrolyte balance. However, this Phase I drug is being studied to inhibit aldosterone synthase itself, blocking the production of aldosterone. Currently approved drugs only block aldosterone's binding to its nuclear receptor.

Preclinical Pipeline for Hypertension

To predict what may enter the clinical pipeline in the near future, we examined preclinical programs in the Biomedtracker database. We found only five preclinical programs listed with two of these for established targets for approved drugs. Two programs were targeting aminopeptidase A and another program had an undisclosed target.

Trends in Clinical Trial Initiations in Hypertension

To assess investment and general pipeline activity across the industry, we quantified the number of clinical programs started each year for the last decade. From 1,071 hypertension tagged trial starts found in the TrialTrove database, we categorized trials for novel drugs (NCEs), vs. nonintervention trials, reformulations, combinations of older drugs and other duplicate trials per Phase, identifying 54 novel drug intervention trial starts over the 10-year period. The majority of trials in the database were for generics and for different trial arms, trial sites, or recruitment parameters for the same drug program.

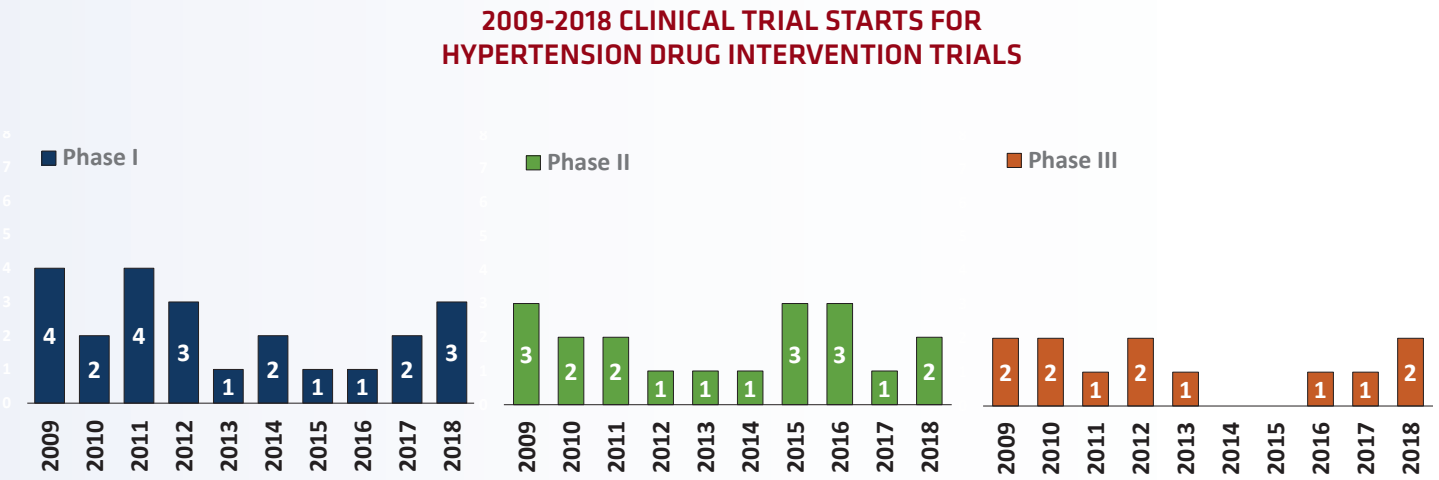
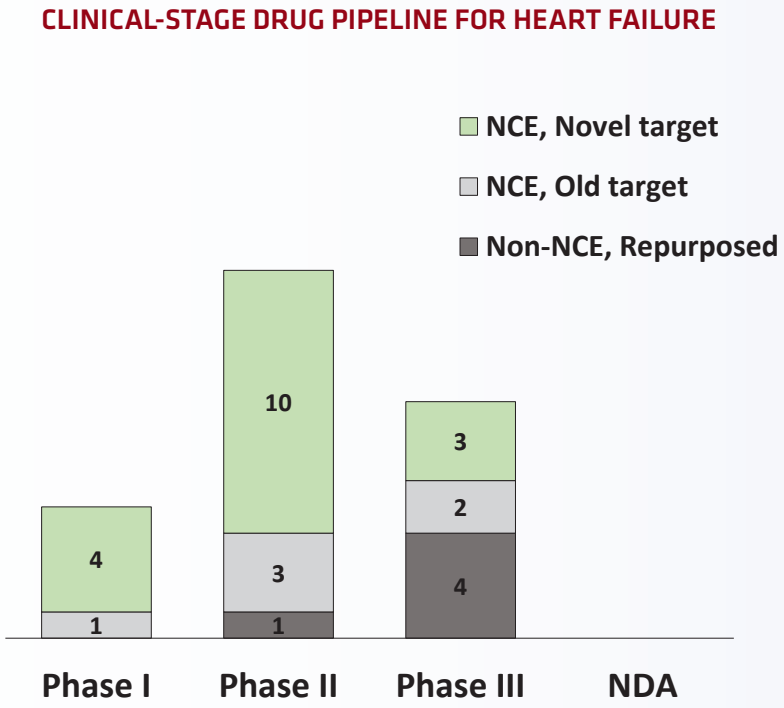


Figure 9. Clinical trial starts for novel drugs for hypertension, 2009-2018. TrialTrove data accessed September 2019. A total of 1,071 clinical trial starts were retrieved from TrialTrove. Trials were individually assessed for NCE intervention trials only and trial Phase cohorts de-duplicated. A total of 54 novel drug intervention trials were initiated during this time period.

As shown in **Figure 9,** clinical trial starts involving potential hypertension drugs remained in an average range of only one or two per year for each of the three Phases. As might be expected based on attrition rates, more starts were found in Phase I (23) vs. Phase II (19) and Phase III (12). There were two years in which not a single NCE Phase III trial was initiated. Many of the drug intervention trials in the database were for NCEs targeting previously established mechanism of action.

Clinical Pipeline for Heart Failure

There are currently 28 clinical programs for heart failure. Of these 28, 23 are new chemical entities (NCEs) and five are repurposed diabetes drugs. Six of the NCEs are for targets and mechanisms that have already received FDA approval and 17 NCEs have novel targets, as shown in **Figure 10.** For the pipeline of NCEs with new targets, more than half are in Phase II and three are in Phase III. The remaining four are in Phase I. The new targets can be classified into four approaches: restoration of heart muscle contractibility, regeneration of heart cells, decrease inflammation of heart tissue, and vasodilation.



Novel target for CHF	Phase I	Phase II	Phase III	NDA
myosin	0	1	1	0
stem cells	0	1	2	0
ERBB4/ERBB2	0	1	0	0
VEGF (mRNA)	0	1	0	0
AC6 (gene therapy)	0	1	0	0
DPP-IV	0	1	0	0
myeloperoxidase	0	1	0	0
vasopressin receptors	0	1	0	0
PDE1	0	1	0	0
Aminopeptidase A	0	1	0	0
relaxin	1	0	0	0
mTORC-1	1	0	0	0
GPCR autoantibodies	1	0	0	0
not disclosed (gene therapy)	1	0	0	0
Total	4	10	3	0

Figure 10. The currently active hypertension disease clinical pipeline by Phase (as of September 2019), based on Biomedtracker's classification methodology by Phase of development as well as company website information. Programs listed as "Ex-U.S." in the Biomedtracker database are included here by Phase based on independent research of company websites. This "Ex-U.S." listing implies the companies have not yet intended to seek FDA approval. Right: The number of programs in each of the target strategies by clinical Phase.

Heart muscle contractibility clinical programs for heart failure

Of the drug programs focused on heart muscle cell functioning, the most advanced NCE programs target cardiac myosin, one in Phase III and the other in Phase II. Both aim to increase cardiac output during systole contraction while retaining diastole relaxation and filling. They both bind to myosin allosterically (away from the active site of the enzyme) to enhance actin interaction generating more force in heart muscles.

There are two gene therapy programs in the clinic. The most advanced is a single dose viral gene therapy in Phase II that introduces adenylyl cyclase type 6 gene directly into heart muscle. The adenylyl cyclase gene is down regulated in heart failure patients and the added gene is aiming to compensate for those lower levels. Adenylyl cyclase is responsible for cAMP production, a requirement for muscle contraction.[8] A non-viral gene therapy in Phase I is designed to express three different human proteins to benefit cardiomyocytes.

A peptide fragment of neuregulin-1 beta 2 alpha (rhNRG-1β2α) is in Phase II for heart failure with reduced ejection fraction (HFrEF). This works on ErbB4/B2 receptors to promote sarcomere structural re-organization, with the goal of increasing cardiac contractility and relaxation.

Regeneration and repair clinical programs for heart failure

Three stem cell approaches are found in the heart failure clinical pipeline, two in Phase III and one in Phase II: One Phase III program uses the patient's own bone marrow cells (autologous cells) for the treatment of heart failure that develops after a heart attack. The other Phase III program uses single source stem cells ("off-the-shelf" or allogeneic cells) that are delivered to the heart. The Phase II cell therapy program also uses allogeneic cells to treat heart failure patients. These stem cell approaches are also believed to have anti-inflammatory effects on damaged heart tissue in addition to the potential regeneration of heart tissue.

An mRNA therapy is in Phase II for heart failure. The modified mRNA produces vascular endothelial growth factor (VEGF), a well-studied protein that is known to control angiogenesis. The expectation with these studies is to observe cardiac regeneration and increase blood flow in the hearts of trial participants.

An inhibitor of dipeptidyl peptidase IV (DPP-IV), a validated target for treating diabetes, is under investigation in Phase II. These drugs boost the half-life of GLP-1, stromal derived factor-1α (SDF-1α), and other peptides circulating in the blood, believed to have a beneficial effect on damaged heart tissue in heart failure patients that have experienced myocardial infarction.

A clinical study is underway to test a small molecule inhibitor of phosphodiesterase 1 (PDE1). This target's mechanism is slightly different than the approved drug targets, PDE3 and PDE4, due to its location within heart muscle cells and influence on signaling cascades involving calcium. Inhibition of PDE1 is thought to promote survival of cardiomyocytes.[9]

[8] Gau, M., et al. Beneficial Effects of Adenylyl Cyclase Type 6 (AC6) Expression Persist Using a Catalytically Inactive AC6 Mutant. Mol Pharmacol. 79 (3) 381–388 (2011)
[9] Leroy, J., et al. Inhibit a Phosphodiesterase to Treat Heart Failure? Circulation. 138 (18) 2003-2006 (2018)

Anti-inflammatory clinical programs for heart failure

The first treatment addressing an autoimmune basis for certain types of heart failure is in Phase II. The chemical entity for this program is a DNA aptamer that neutralizes autoantibodies directed against GPCR beta-1 adrenergic receptor. As described previously, the beta-adrenergic receptors are critical in regulating heart rate. When autoantibodies bind to these receptors on the heart, damage and even cell death can occur leading to heart failure.[10]

A derivative of rapamycin is in Phase I development for the treatment of heart failure with preserved ejection fraction (HFpEF). This mTORC1 inhibitor is being developed for a range of age-related diseases that are due to a decline in immune function.

A myeloperoxidase inhibitor is in Phase II. This peroxidase enzyme target can be found in white blood cells and its activity is linked to chronic inflammation-related cardiovascular disease (including impaired vascular endothelial function and fibrosis).[11]

Vasodilation clinical programs for heart failure

A dual-acting vasopressin receptor antagonist is in Phase II. Increased plasma vasopressin levels are associated with the progression of congestive heart failure. Vasopressin mediates water retention in the kidney through its V2 receptor, as well as vasoconstriction, cardiac hypertrophy, and fibrosis through its V1 receptor. Its diuretic activity is outside the direct renin, angiotensin, aldosterone pathway blockers that are on the market.

An engineered relaxin protein is in Phase 1. Like the naturally occurring version of the peptide hormone, it has the potential to improve cardiac function through the production of nitric oxide, and thus vasodilation.[12] Previous versions of relaxin have been tested for acute heart failure, but never reached the market.

The same aminopeptidase A inhibitor found in the hypertension pipeline (discussed previously) is also in Phase II for heart failure.

Repurposed drugs in the pipeline for heart failure

There are six repurposed drugs in the pipeline for heart failure. Four of these are SGLT2 inhibitors (Invokana, Farxiga, Jardiance, and Zynquista) all in Phase III. An endothelin receptor type A/B antagonist approved for pulmonary arterial hypertension, Opsumit, is in Phase II to evaluate reductions in cardiovascular biomarkers in patients with preserved ejection fraction (HFpEF) and pulmonary vascular disease.

Preclinical programs for heart failure

To predict what may enter the clinical pipeline soon, we examined novel preclinical programs in the Biomedtracker databases. We found that five of the 15 preclinical programs listed had unique targets not currently in the clinic (free fatty acid receptors, IL-11 receptors, IL-1, galactin, and ATP binding cassette subtype C) and four were undisclosed.

[10] https://berlincures.de/berlin-cures-set-to-launch-Phase-2-study-of-heart-failure-drug. Accessed December 1, 2019.

[11] Gan, L., et al. Safety, tolerability, pharmacokinetics and effect on serum uric acid of the myeloperoxidase inhibitor AZD4831 in a randomized, placebo-controlled, Phase I study in healthy volunteers. Br J Clinical Pharmacology. 85 (4), 762–770 (2019)

[12] Tousoulis, D., et al. The role of nitric oxide on endothelial function. Curr Vascular Pharmacology. 10, 4–18 (2012) and Teerlink, J., et al. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomized, placebo-controlled trial. The Lancet. 381, 9860 (2013)

Trends in Clinical Trial Initiations in Congestive Heart Failure

From 478 heart failure tagged trial starts found in the TrialTrove database, we categorized trials for novel drugs (NCEs) vs. nonintervention trials, reformulations, combinations of older drugs and other duplicate trials per Phase, identifying 76 novel drug intervention trial starts over the 10-year period. The majority of trials in the database were for generics and for different arms, trial sites, or recruitment parameters for the same drug program.

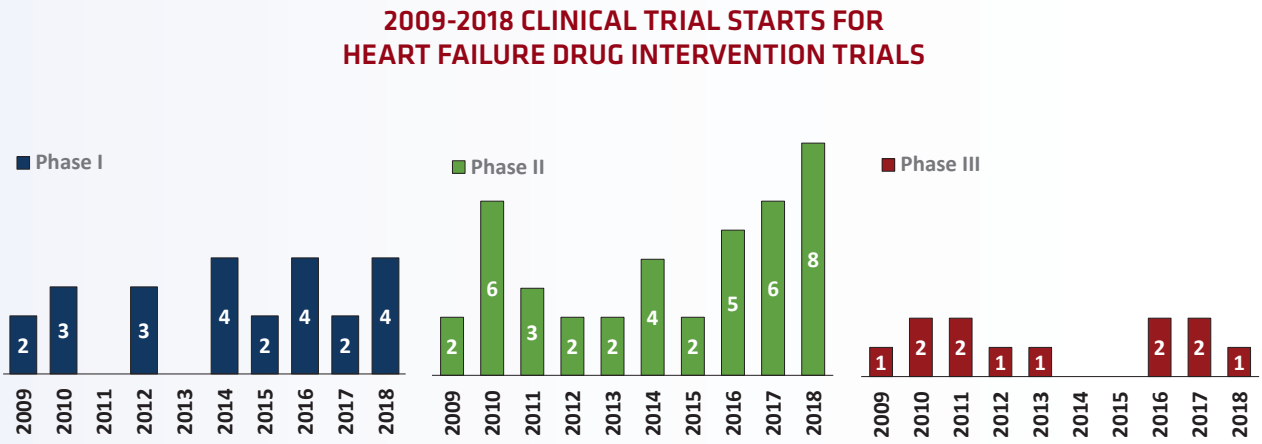


Figure 11. Clinical trial starts for novel drugs for heart failure, 2008-2019. TrialTrove data accessed October 2019. A total of 478 clinical trial starts were retrieved from TrialTrove. A total of 76 novel drug intervention trials were initiated during this time period.

As shown in **Figure 11,** Phase II trial starts have increased substantially from a low of two in 2009 to eight in 2018, suggesting an increased focus on innovative R&D. Phase I trial starts for NCEs, although lower in number vs. Phase II, have doubled in the last five years vs. the previous five years (from 8 to 16). However, Phase III trial starts have remained at two or less per year over the last decade.

Discussion

Cardiovascular disease in both developed and developing nations is growing. Total healthcare and economic costs to society are expected to grow to $1.1 trillion by 2035.[13] Solving for this coming crisis should be front and center of policy initiatives aimed at reducing future economic societal burden. Future therapeutic interventions offer a solution for managing the progression of highly prevalent cardiovascular diseases.

Although there are numerous generic drugs available for systemic hypertension, potential side effects and sub-optimal efficacy challenges remain for a subset of patients. Unfortunately, the current drug pipeline is lacking in volume and breadth to fully match this unmet need. Of the 18 ongoing clinical programs in hypertension, only six are NCEs with novel mechanisms of action. Most of these are still in early development, with only one program in Phase III. Pivotal clinical trial initiations involving novel drugs for systemic hypertension have averaged only one per year over the last five years. Based on high attrition rates observed for novel cardiovascular drugs (**Figure 4**), only one of these novel pipeline programs will likely reach FDA approval. Furthermore, most of the novel targets in the pipeline overlap with existing drug intervention mechanisms or pathways, such as those along the RAAS and adrenergic system.

Within heart failure, most approved drugs have demonstrated clinical efficacy for a type of heart failure that accounts for only half of the diagnosed cases of left-sided heart failure.[14] Patients experiencing heart failure with preserved ejection fraction (HFpEF) illustrate a remaining unmet need for this indication. Of 23 ongoing clinical drug programs for heart failure, there are 18 NCEs for novel targets. While this is three times as many programs than hypertension, likely addressing the greater unmet medical need in heart failure, this total number remains far below the number of novel clinical programs found in a single sub-indication for oncology. For example, breast cancer has 158 NCE clinical development programs, lung cancer has 180, and leukemias have 211.[15] Other cardiovascular indications, such as coronary artery disease (the number one cause of death in the U.S.) also suffer from a small clinical pipeline of NCEs (**Appendix A1**) and relatively little growth has been seen over the last five years across all cardiovascular indications (**Figure 3**).[16]

The main obstacles for expanding the cardiovascular pipeline include the inability to stratify patient populations, lack of understanding of the pathophysiology behind certain subtypes of the disease, challenging and costly regulatory requirements, and a difficult reimbursement environment.

More effort upstream is needed to understand the heterogeneity within these large target populations of cardiovascular disease. It has been known for some time that certain ethnic groups suffer disproportionately with heart disease. For example, African Americans are 20 times more likely to develop heart failure before the age of 50 than Caucasians.[17] Hypertension is also known to have a hereditary component, as it has been known to run in families and has recently been correlated to as many as 500 gene regions.[18] These findings suggest complex underlying genetic risk factors for developing certain types of hypertension and heart failure. The ability to stratify this heterogeneous population would help identify patients for enrollment into appropriately designed trials.

[13] Benjamin, E., et al. Heart Disease and Stroke Statistics—2018 Update: A Report from the American Heart Association. Circulation. 137 (12) (2018)

[14] The two main subtypes of heart failure are 1) heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF)

[15] Data for oncology R&D pipeline is taken from the Biomedtracker database, NMEs and novel biologics only, and current as of January 2019. A total count by disease area can be found in Thomas, D., Wessel, C. BIO Industry Analysis. Emerging Company Trend Report, (2018) (www.bio.org/iareports)

[16] American Heart Association. Heart Disease and Stroke Statistics-2019 At-a-Glance. (2019) https://healthmetrics.heart.org/wp-content/uploads/2019/02/At-A-Glance-Heart-Disease-and-Stroke-Statistics-%E2%80%93-2019.pdf

[17] Bibbins-Domingo, K., et al. Racial differences in incident heart failure among young adults. N Engl J Med. 360 (12),1179-1190 (2001)

[18] Evangelos, E. et al. Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. Nature Genetics. 50, 1412–1425 (2018)

For hypertension, few predictive biomarkers currently exist to help identify subtypes of the disease or identify a root cause of the disease. In fact, the majority of hypertension cases are still of unknown cause.[19] Within heart failure, advanced imaging technologies have been developed to correctly identify subtypes of heart failure at the macroscopic level (for example, to determine ejection fraction from the left ventricle and levels of strain by echocardiography), but typically only after the disease has progressed. Although a few biomarkers exist for ruling out heart failure diagnosis (such as the natriuretic peptides, BNP and NT-proBNP), more biomarkers are needed to identify subtypes of the disease early in the progression to improve future outcomes. As patients become more equipped with digital devices, the correlation of real-world data tracking with circulating biomarkers and genetic sequence data may lead to new discoveries of patient subpopulations responsive to specific types of treatment.

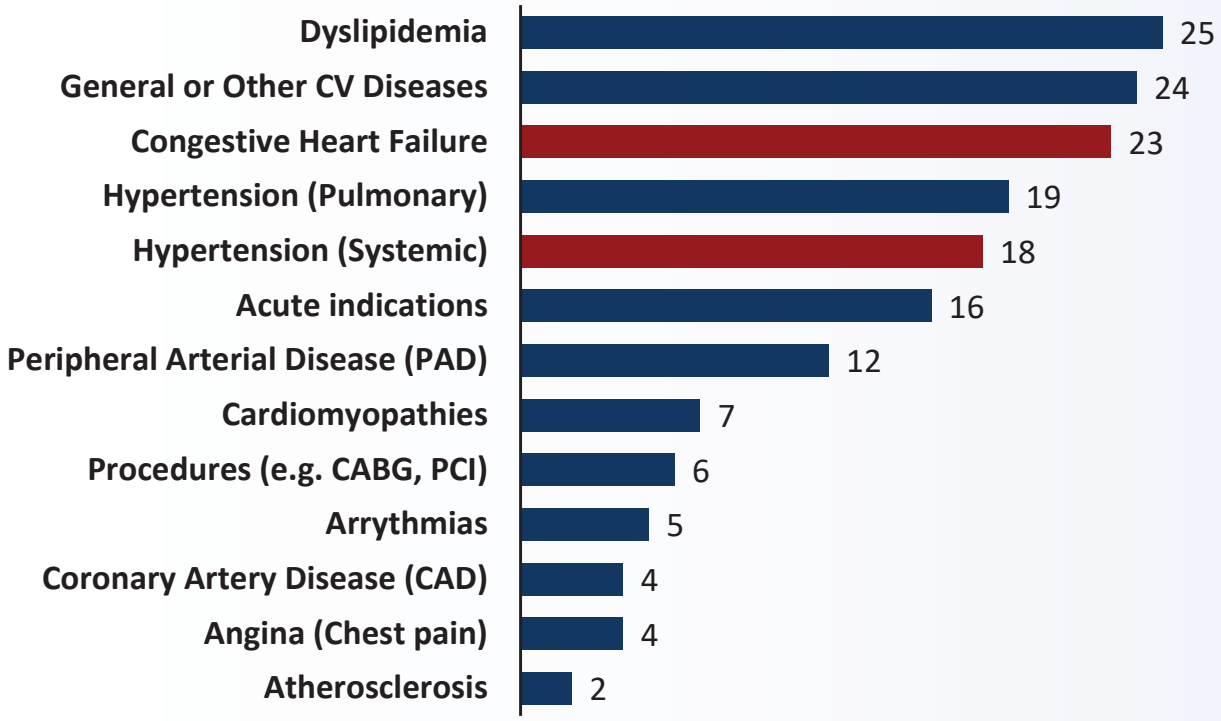
Regulatory hurdles for pivotal studies in cardiovascular disease remain. A single cardiovascular outcome study of 10,000 patients can take five years to conduct with only a 50.9% chance of success (**Figure 4**). Recently issued FDA guidance on clinical endpoints required for approval in heart failure acknowledges the hurdle the industry is facing and takes steps to address the issue, but additional clarity on pivotal trial requirements for new drugs with novel targets is needed.

The majority of hypertension and heart failure drugs on the market are available as generics. Payor resistance to creating a streamlined reimbursement environment for innovative cardiovascular drugs has caused investors to pull back from investment in novel cardiovascular therapies.

The Biotechnology Innovation Organization (BIO) and member companies view innovation as the key to helping patients with cardiovascular disease. Advancements in science, more choices for patients, and a policy environment that stimulates greater investment in R&D are necessary to achieve this goal.

[19] Primary (or "essential") hypertension makes up roughly 90% of high blood pressure cases and has been linked to diet, salt balance, lack of exercise and obesity, but is not attributed to any specific genes or condition as the root cause. Secondary hypertension, however, is of known cause – typically other disease conditions of the kidneys, arteries, heart or endocrine system. Charles, L., et al. Secondary Hypertension: Discovering the Underlying Cause. Am Fam Physician. 96 (7), 453-461 (2017)

Appendix



A1. Clinical-stage NCE programs for all cardiovascular Indications in the Biomedtracker database.

Bio Industry Analysis

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