BME Graduate Introduction

Cardiovascular Challenges and Opportunities for Biomedical Engineering

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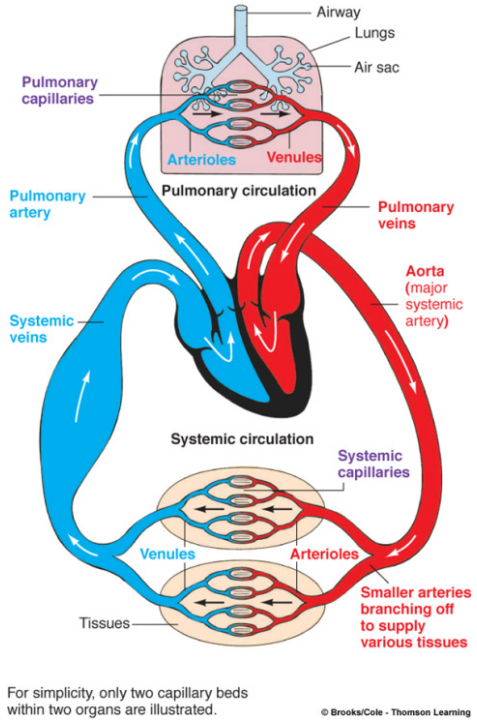

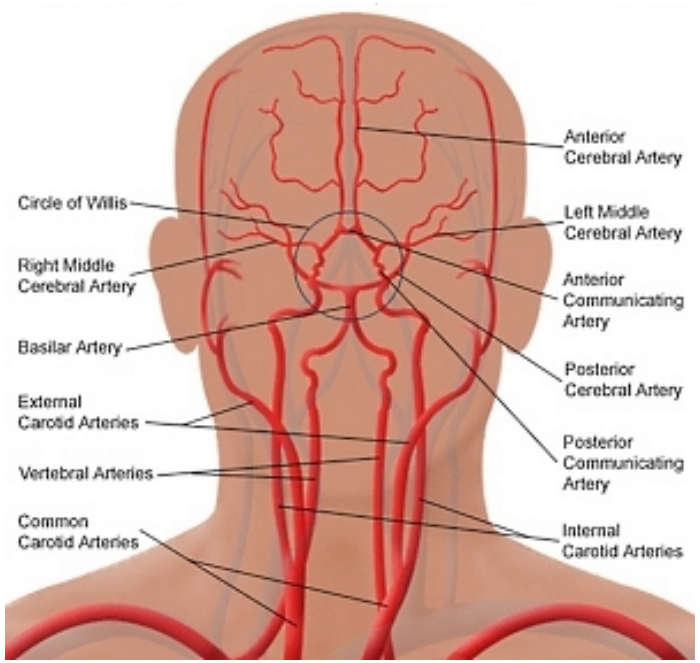

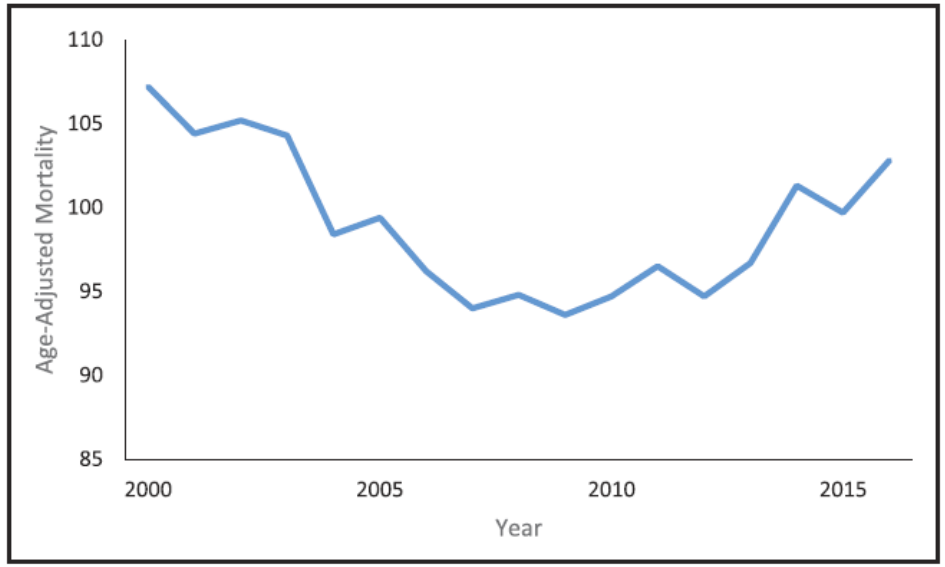

Figure 2. Rising cardiovascular disease mortality rates for people who are living in rural areas, middle-aged (45–54 years of age), and white. Authors' analysis using data from the National Vital Statistics System.[3]

Cardiovascular disease, mortality & burden 2015.

Table 1. Common Cardiovascular Diseases, Related Mortality, and Disease Burden in 2015

	Total Number of Estimated Deaths 2015 Globally (Thousands)	Cumulative Percentage of CVD Deaths	Age-Standardized Death Rate (per 100 000 Person-Years)	Ranking Based on Disease Burden (Measured by DALYs)
All deaths	55 792		850	
All cardiovascular deaths	17 921	100%	285	
Ischemic heart disease	8917	49.8%	142	1
Cerebrovascular disease	6326	85.1%	101	2, hemorrhagic/other stroke 3, ischemic stroke
Hypertensive heart disease	962	90.4%	15.4	4
Cardiomyopathy and myocarditis	353	92.4%	5.4	7
Rheumatic heart disease	319	94.2%	4.8	6
Atrial fibrillation	195	95.3%	3.3	8
Aortic aneurysm	168	96.2%	2.7	9
Endocarditis	84	96.7%	1.3	10
Peripheral vascular disease	52	97.0%	0.9	11
Other cardiovascular	541	100.0%	8.6	5

CVD indicates cardiovascular diseases; and DALY, disability-adjusted life years.
Data derived from GBD 2015 Mortality and Causes of Death Collaborators[3] and Roth et al.[8]

Joseph P, Leong D, McKee M, et al. Reducing the Global Burden of Cardiovascular Disease, Part 1: The Epidemiology and Risk Factors. *Circ Res.* 2017;121(6):677-694.

Risk factors.

Table 2. Predominant Risk Factors for Myocardial Infarction and Stroke Based on the INTERHEART and INTERSTROKE Studies[30,31]

	Myocardial Infarction			Stroke		
	Rank	Odds Ratio	PAR	Rank	Odds Ratio	PAR
ApoB/ApoA1 ratio	1	3.25	49.2	3	1.84	26.8
Smoking	2	2.87	35.7	7	1.67	12.4
Psychosocial factors*	3	2.67	32.5	6	2.20	17.4
Abdominal obesity	4	1.62	20.1	5	1.44	18.6
Self-report of hypertension	5	1.91	17.9	1	2.98	47.9
Healthy diet†	6	0.70	13.7	4	0.60	23.2
Physical activity	7	0.86	12.2	2	0.60	35.8
Self-report of diabetes mellitus	8	2.37	9.9	10	1.16	3.9
Regular alcohol consumption	9	0.91	6.7	9	2.09	5.8
Cardiac causes	NA	NA	NA	8	3.17	9.9

Apo indicates apolipoprotein; NA, not applicable; and PAR, population attributable risk.

*Only partly confirmed in prospective studies.

†Dietary measure in INTERHEART was daily fruit and vegetable consumption and in INTERSTROKE was measured using the modified Alternative Healthy Eating Index.

Joseph P, Leong D, McKee M, et al. Reducing the Global Burden of Cardiovascular Disease, Part 1: The Epidemiology and Risk Factors. *Circ Res.* 2017;121(6):677-694.

Troubling evidence between ~2012 to 2019.

Circulation

February 26, 2019

AHA PRESIDENTIAL ADVISORY

Call to Action: Urgent Challenges in Cardiovascular Disease

A Presidential Advisory From the American Heart Association

ABSTRACT: Although advances in care have spurred improvements in cardiovascular outcomes, cardiovascular disease remains the leading cause of death in the United States and around the world. Previous declines in cardiovascular disease mortality have slowed and even reversed for certain demographics. Further concerns exist with regard to cardiovascular drug innovation, quality of care, and healthcare costs. The Value in Healthcare Initiative–Transforming Cardiovascular Care, a collaboration of the American Heart Association and Duke University, Robert J. Margolis, MD, Center for Health Policy, aims to increase access to and affordability of cardiovascular treatment and to decrease barriers to care. The following Call to Action describes trends in cardiovascular care, identifies gaps in areas of cardiovascular disease prevention and treatment, highlights challenges with medical product innovation, and finally, outlines a series of learning collaboratives that will aid in the development of road maps for transforming cardiovascular care.

Mark McClellan, MD, PhD
Nancy Brown, BS
Robert M. Califf, MD, MACC
John J. Warner, MD, FAHA

Ischemic heart disease mortality with achievements and initiatives.

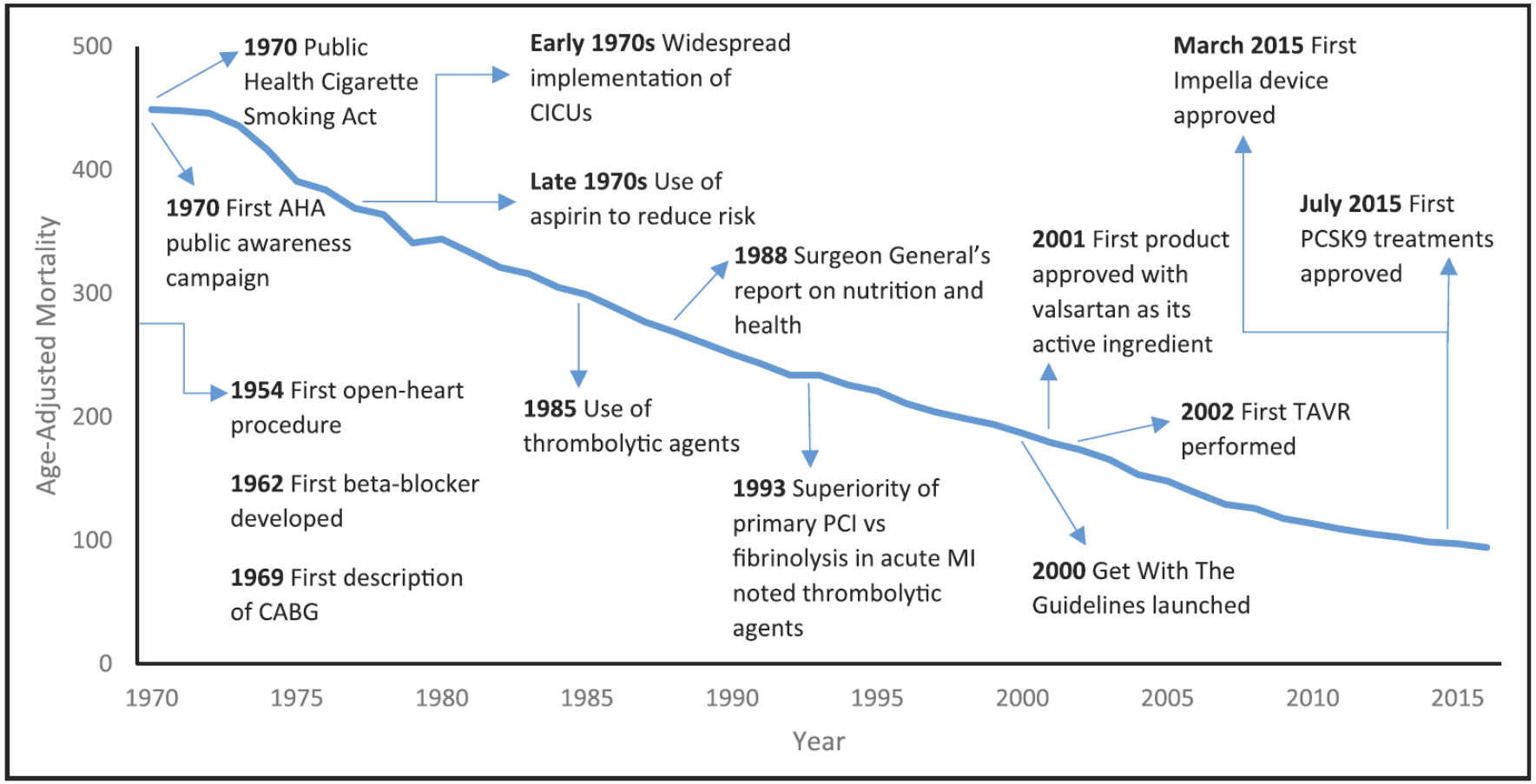

Figure 1. Ischemic heart disease mortality over time with selected medical advancements and public health initiatives.
AHA indicates American Heart Association; CABG, coronary artery bypass grafting; CICU, cardiac intensive care unit; MI, myocardial infarction; PCI, percutaneous coronary intervention; PCSK9, proprotein convertase subtilisin/kexin type 9; and TAVR, transcatheter aortic valve replacement. Mortality data and selected intervention dates are drawn from prior work by Nabel and Braunwald[2] with recent mortality data drawn from the National Vital Statistics System.[3,3a]

McClellan et al. Urgent Challenges in Cardiovascular Disease. Circulation. 2019;139:e44–e54. DOI: 10.1161/CIR.0000000000000652
2. Nabel EG, Braunwald E. A tale of coronary artery disease and myocardial infarction. N Engl J Med. 2012;366:54–63. doi: 10.1056/NEJMra1112570
3. Centers for Disease Control and Prevention. Underlying cause of death 1999–2017: CDC WONDER Online Database. https://wonder.cdc.gov/wonder/help/ucd.html. 2018. Accessed December 10, 2018.
3a. Cribier AG. The odyssey of TAVR from concept to clinical reality. Tex Heart Inst J. 2014;41:125–130. doi: 10.14503/THIJ-14–4137.

Steven S. Saliterman

Cardiovascular mortality is no longer falling.

- CVD is the leading cause of death 17.3 million globally per year, projected to 23.6 million by 2030.
- Age adjusted mortality has remained flat in recent years.
- Decline in CHF in hospital patients is also leveling off.
- Declines in age-adjusted stroke mortality have simililary plateaued.

Actually rising in rural areas.

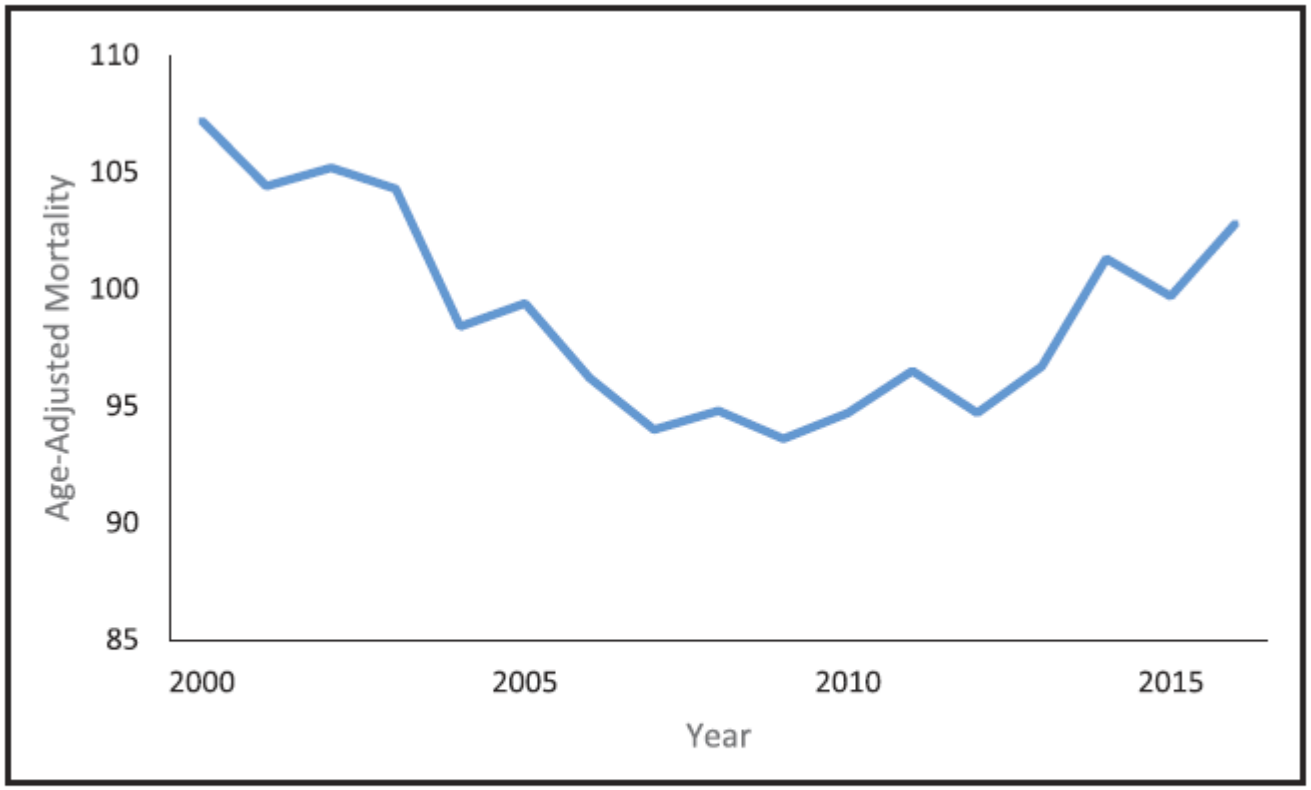

Figure 2. Rising cardiovascular disease mortality rates for people who are living in rural areas, middle-aged (45–54 years of age), and white.
Authors' analysis using data from the National Vital Statistics System.[3]

3. Centers for Disease Control and Prevention. Underlying cause of death 1999–2017: CDC WONDER Online Database. https://wonder.cdc.gov/wonder/help/ucd.html. 2018. Accessed December 10, 2018.

Cardiovascular health disparities persist.

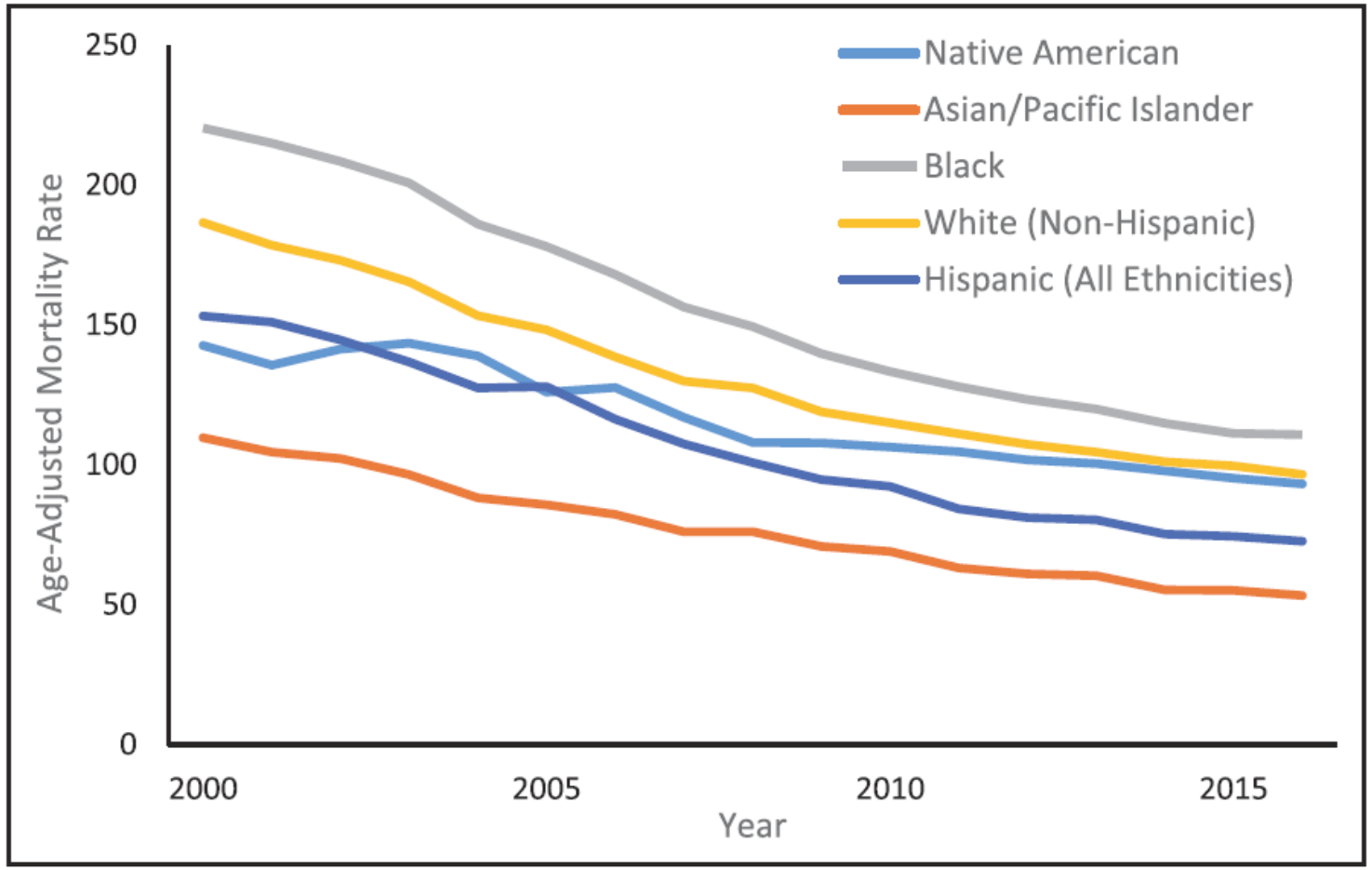

Figure 3. Disparities among ischemic heart disease mortality by race and ethnicity.
Authors' analysis using data from the National Vital Statistics System.[3]

3. Centers for Disease Control and Prevention. Underlying cause of death 1999–2017: CDC WONDER Online Database. https://wonder.cdc.gov/wonder/help/ucd.html. 2018. Accessed December 10, 2018.

The value of cardiovascular care is declining.

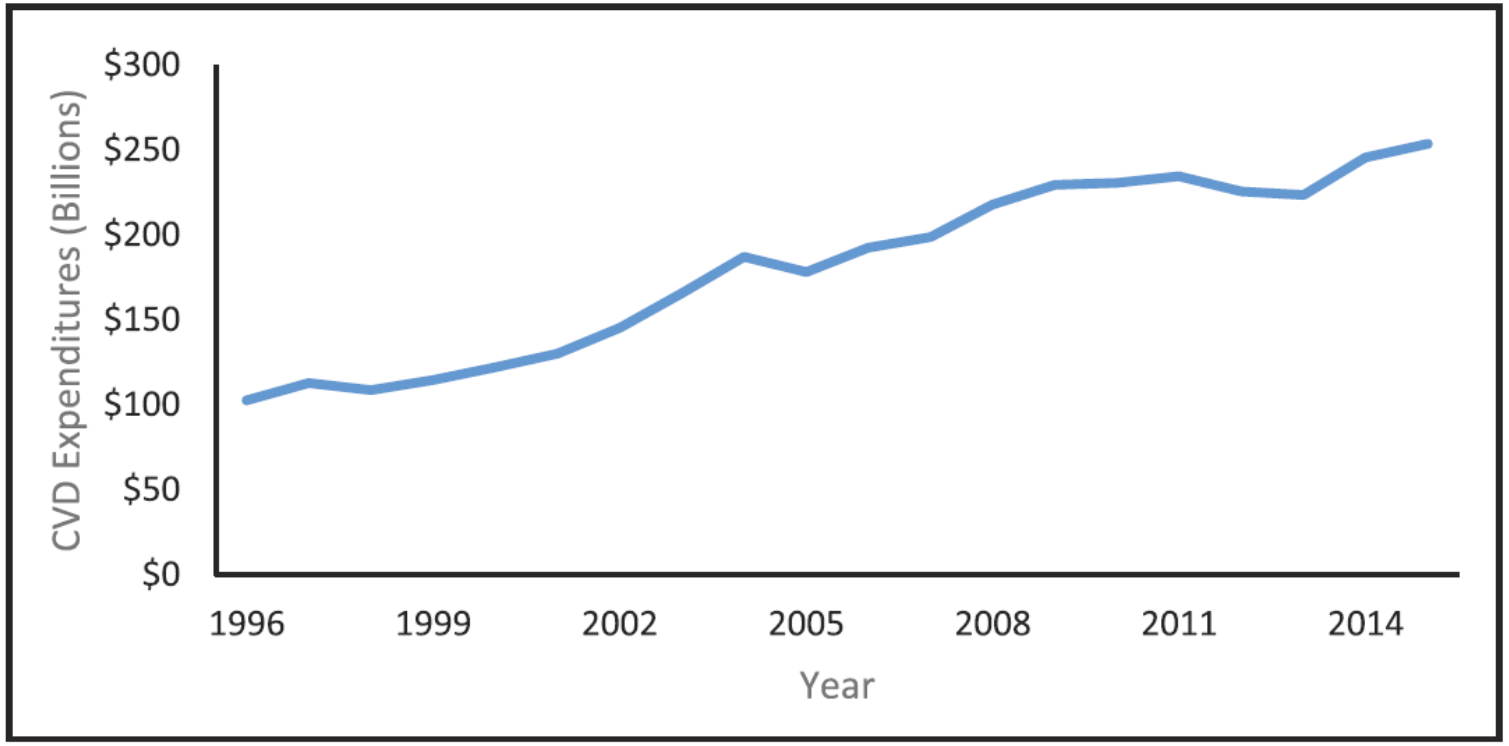

Figure 5. Overall spending on cardiovascular disease (CVD) care over time (based on self-reports of disease conditions).
Authors' analysis using data from the Medical Expenditure Panel Survey.[17]

- $318 billion spent in 2015 for all aspects of CVD.

McClellan et al. Urgent Challenges in Cardiovascular Disease. Circulation. 2019;139:e44–e54. DOI: 10.1161/CIR.0000000000000652
17. Agency for Healthcare Research and Quality. MEPS summary tables. https://meps.ahrq.gov/mepstrends/home/index.html. Accessed October 23, 2018.

Missed opportunities.

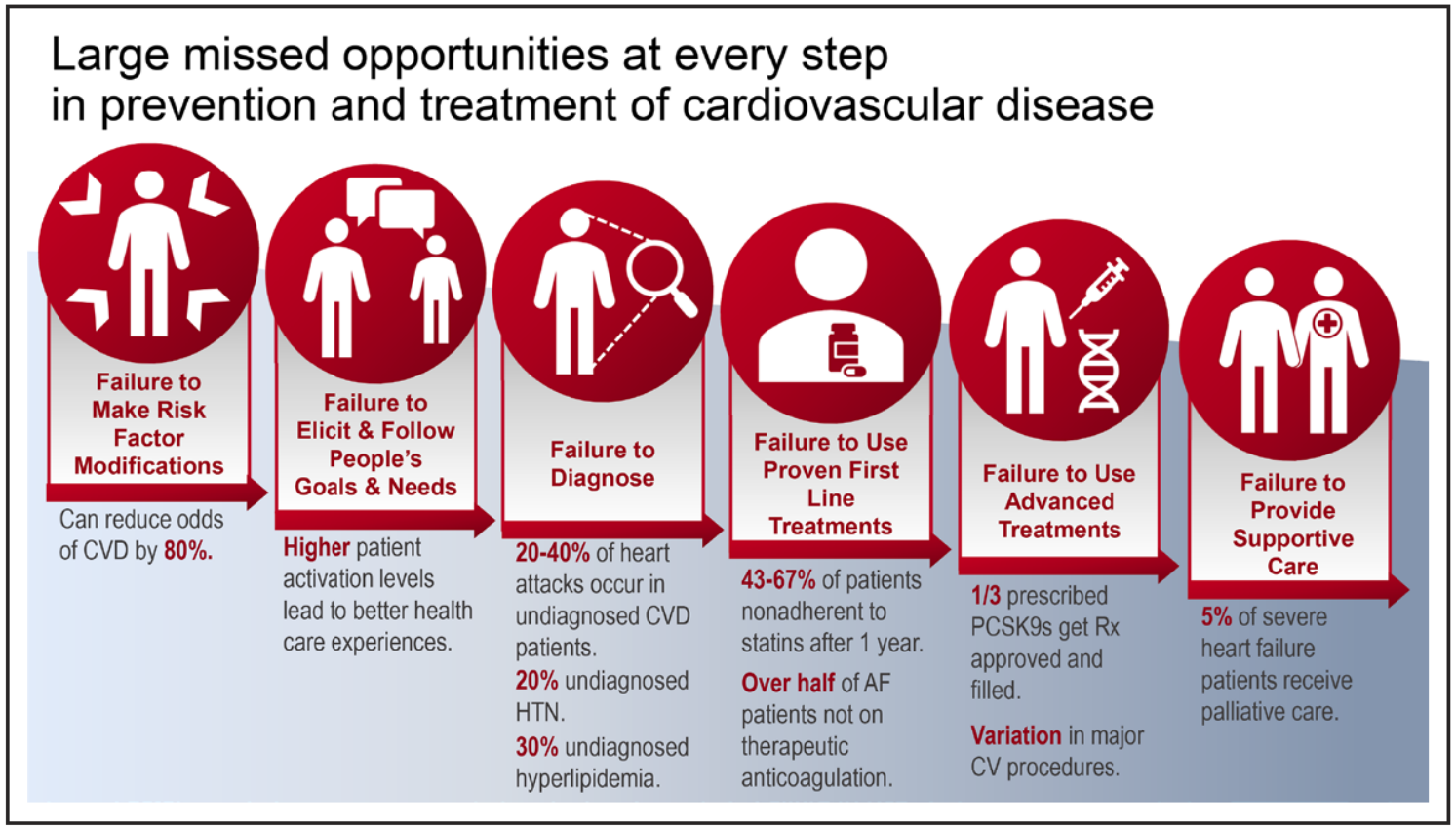

Figure 6. Cardiovascular care challenges waterfall showing the challenges at each stage of the disease continuum.
AF indicates atrial fibrillation; CV, cardiovascular; CVD, cardiovascular disease; HTN, hypertension; Rx, prescription; and PCSK9, proprotein convertase subtilisin/kexin type 9. Data derived from Yusuf et al,[32] Hibbard and Greene,[33] Dalen et al,[34] Zallman et al,[35] Turin et al,[36] Pokorney et al,[37] Navar et al,[38] and Warraich et al.[39]

McClellan et al. Urgent Challenges in Cardiovascular Disease. Circulation. 2019;139:e44–e54.
DOI: 10.1161/CIR.0000000000000652

Effects of prevention on premature mortality attributable to cv disease risk factors.

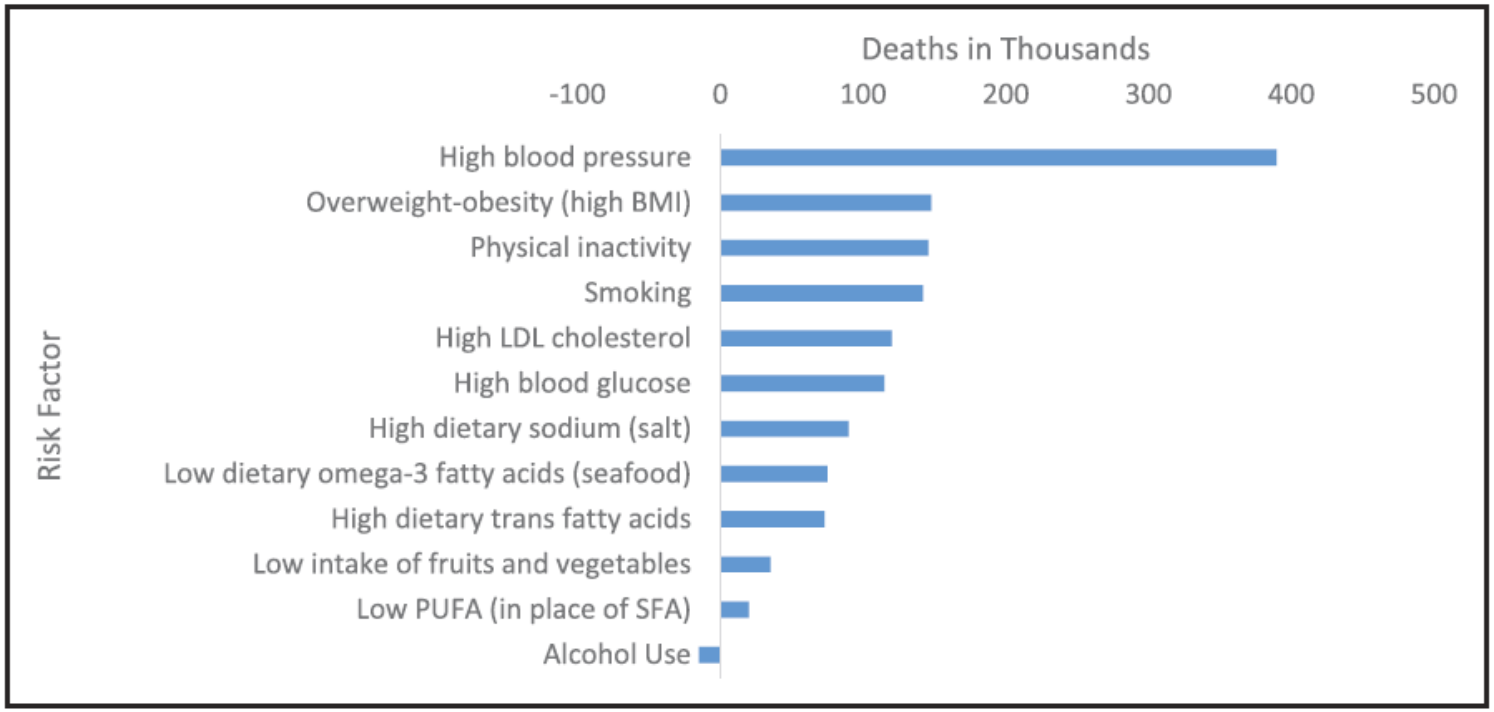

Figure 7. Effects of prevention on premature mortality attributable to cardiovascular disease risk factors.
BMI indicates body mass index; LDL, low-density lipoprotein; PUFA, polyunsaturated fatty acid; and SFA, saturated fatty acid. Data derived from Danaei et al.[40]

40. Danaei G, Ding EL, Mozaffarian D, Taylor B, Rehm J, Murray CJ, Ezzati M. The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. PLoS Med. 2009;6:e1000058. doi: 10.1371/journal.pmed.1000058

The medical device industry may be on the brink.

- These risk factors call for a shift toward more upstream prevention rather than the current emphasis on down-stream treatment.
  - For example, a 10% increase in hypertension treatment could prevent 14 000 deaths each year, and a 10% increase in treating low-density lipoprotein cholesterol or in preventive aspirin could prevent 8000 deaths.

Farley TA, Dalal MA, Mostashari F, Frieden TR. Deaths preventable in the U.S. by improvements in use of clinical preventive services. Am J Prev Med. 2010;38:600–609. doi: 10.1016/j.amepre.2010.02.016

- Although spending on technological changes for cardiovascular care showed high value through the 1990s, with benefits in length and quality of life that far outweighed their costs
- The currently stagnating (or worsening) trends in cardiovascular outcomes along-side higher spending suggest that this trend no longer holds.

Cutler DM, McClellan M. Is technological change in medicine worth it? Health Aff (Millwood). 2001;20:11–29.

Cutler DM, McClellan M, Newhouse JP, Remler D. Are medical prices declining? Evidence from heart attack treatments. Q J Econ. 1998;113:991–1024. doi:10.1162/003355398555801

Cutler D, McClellan M, Newhouse J. The costs and benefits of intensive treatment for cardiovascular disease. National Bureau of Economic Research. 1998. https://www.nber.org/papers/w6514. Accessed January 3, 2019.

Limited innovation in cardiovascular medical products.

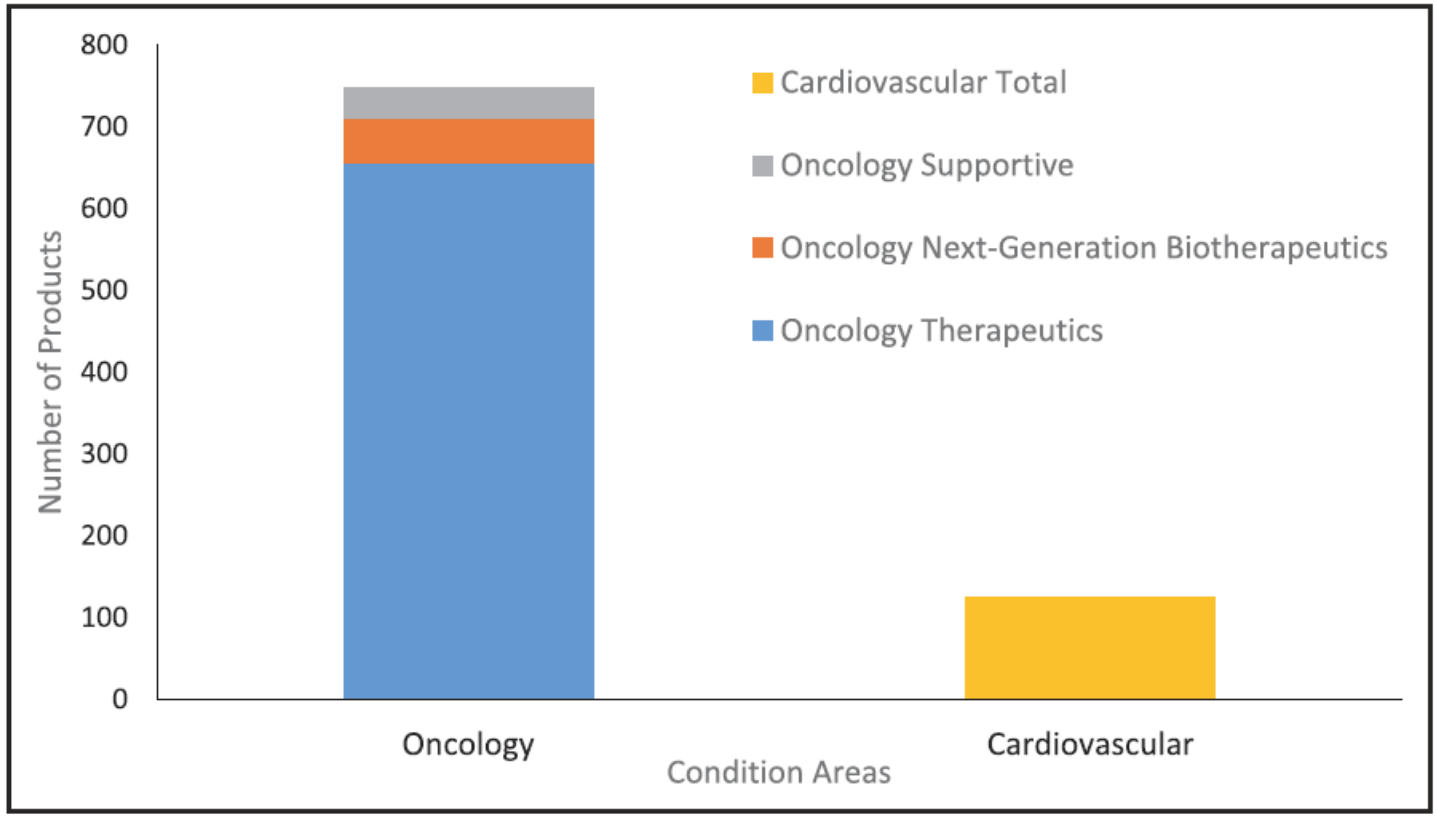

Figure 8. 2017 Late-phase research and development pipeline for oncology and cardiovascular care in 2017.
Data derived from IQVIA. Medicine Use and Spending in the US: A Review of 2017 and Outlook to 2022.[72]

72. IQVIA. Medicine use and spending in the US: a review of 2017 and out-look to 2022. https://www.iqvia.com/institute/reports/medicine-use-and-spending-in-the-us-review-of-2017-outlook-to-2022. Accessed January 3, 2019.

Development pipeline is flat with no clear path forward.

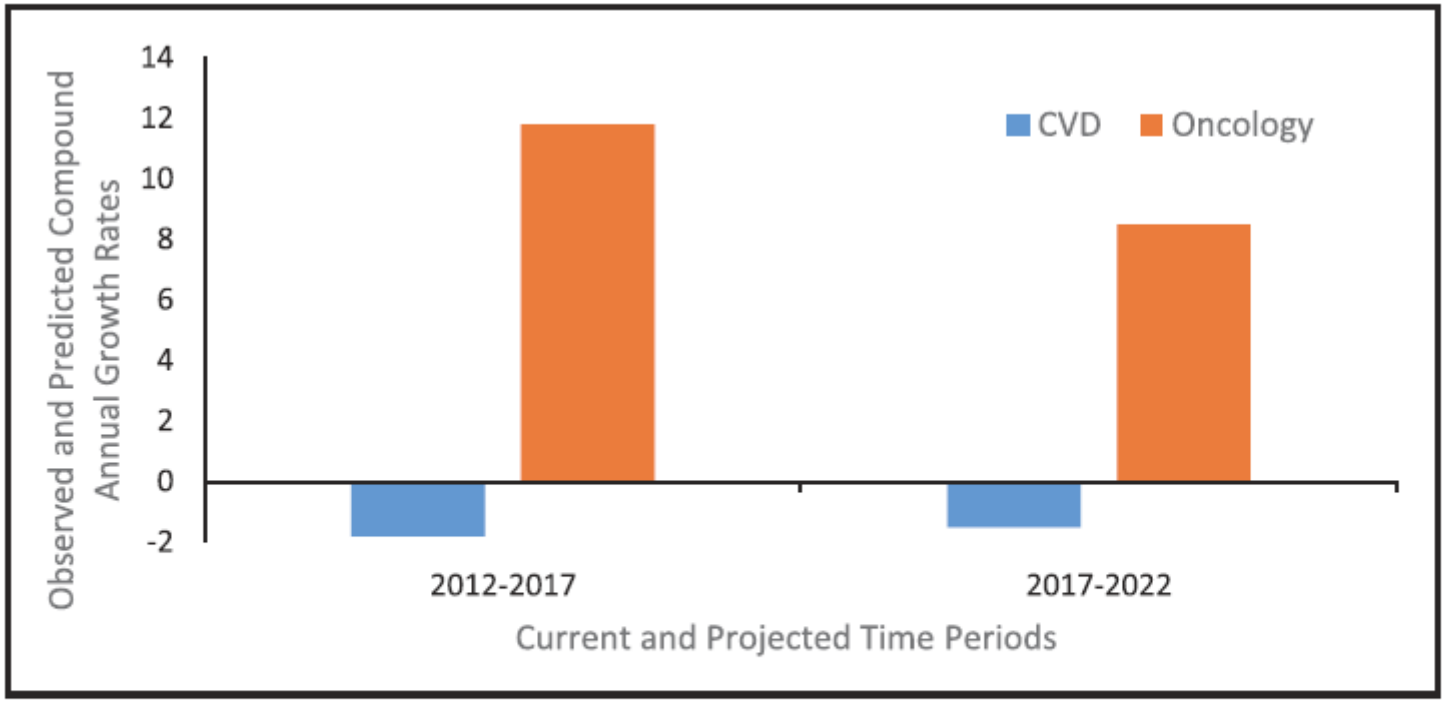

Figure 9. Negative spending growth for cardiovascular products.
CVD indicates cardiovascular disease. Data derived from IQVIA. 2018 and Beyond: Outlook and Turning Points.[80]

80. IQVIA. 2018 and Beyond: outlook and turning points. https://www.iqvia.com/institute/reports/2018-and-beyond-outlook-and-turning-points. Accessed December 12, 2018.

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Perspective

Treatment of chronic heart failure in the 21st century: A new era of biomedical engineering has come

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Conventional medical therapy…

- Administration of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and aldosterone antagonists.

Table 1
Major pharmacotherapy of CHF and related clinical trials.

No.	Types	Drugs	Clinical trials
1	ACEI	Captopril Delapril Enalapril Lisinopril	SOLVD, CONSENSUS, AIRE, SAVE and TRACE
2	ARB	Valsartan Telmisartan Irbesartan	Val-HeFT
3	ARNI	LCZ696 Sacubitril/Valsartan	PARADIGM-HF
4	Beta-blockers	Carvedilol Bisoprolol	US-Carvedilol, CIBIS-II, MERIT-Hf COPERNICUS
5	MRA (aldosterone antagonists)	Spironolactone	TOPCAT ATHENA-HF
6	Other diuretics	Loop diuretics	ASCEND-HF
7	Nitrates	Isosorbide-5-mononitrate (IS5MN)	DRAMI
8	PCSK9 inhibitor	Alirocumab Bococizumab	Uncertain

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9	SGLT2 inhibitors	Canagliflozin	CANDLE trial
		Dapagliflozin	
		Empagliflozin (EMPA)	EMPA-REG trial
10	TCM	Qili qiangxin capsules	
		Qishen yiqi dripping pill (QSYQ)	CACT-IHF
		Shencao tongmai granule (STG)	
		Shenfu injection	
		Shensong yangxin capsules	
11	Other drugs:		
	3,5-diiodothyropropionic acid		
	Cardiac myosin activator		
	Cytokine inhibitors (TNF antagonists)		
	Endothelin antagonists		
	Glycosides		
	Growth hormone		
	Neutral endopeptidase inhibitors		
	NT-proBNP (BNP, nesiritide)	NT-proBNP	PROTECT
	PDE5 inhibitors	Udenafil	ULTIMATE-SHF
	Statins		
	Thyroid hormone analogue		
	Vasopressin antagonism	Tolvaptan	EVEREST

CHF: chronic heart failure; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; MRA: mineralocorticoid-receptor antagonists; PDE5: phosphodiesterase type 5; TCM: Traditional Chinese Medicine; NT-proBNP: amino-terminal pro-B type natriuretic peptide; PCSK9: proprotein convertase subtilisin/kexin type 9; SGLT2: sodium/glucose cotransporter 2; TNF: tumor necrosis factor.

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Engineering opportunities in chronic heart failure.

1. Interventional
2. Mechanical
3. Surgical
4. Tissue
5. Rehabilitation

1. Interventional engineering…

- Percutaneous balloon mitral valvotomy (PBMV)
- Percutaneous coronary intervention (PCI)
- Pacing:
  - Left ventricular pacing (LVP)
  - Biventricular pacing (BiVP) or cardiac resynchronization therapy (CRT)
  - Implantable cardioverter defibrillator (ICD)
  - CRT-ICD (CRT-D) Catheter ablation (AF, VT)

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2. Mechanical engineering…

- Left ventricular assistant device (LVAD)
- VA-ECM OImpella Recover 2.5 (IR2.5)
- Tandem Heart Venoarterial Shunt (VAS)
- Internal artery balloon counter-pulsation (IABP)
- Cardiopulmonary support (CPS)
- Cardiac support device (CSD)
- Total artificial heart (TAH)
- Pulmonary artery pressure sensor
- Interatrial shunt device (IASD)Intravenous inotropic therapy

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3. Surgical engineering…

- Coronary artery bypass graft (CABG)
- Valve surgery (VS)
- Partial left ventriculectomy
- Dynamic cardiomyoplasty
- Myosplint implantation
- Heart transplantation (HT)

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4. Tissue engineering…

- Gene therapy (GT)
- Stem cell transplantation
- Cellular cardiomyoplasty
- Myocardial tissue engineering

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5. Rehabilitating…

- Cardiac rehabilitation (CR)
- External counter-pulsation (ECP)
- Enhanced ECP (EECP)
- Health education
- Psychological interventions
- Home-based hydrotherapeutic
- Thermal program
- Functional electrical stimulation
- Nursing
- Intravenous ferric carboxymaltose (FCM)
- Diet: Flavanol-rich chocolate
- Palliative care

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