

## Chapter 1: Introduction

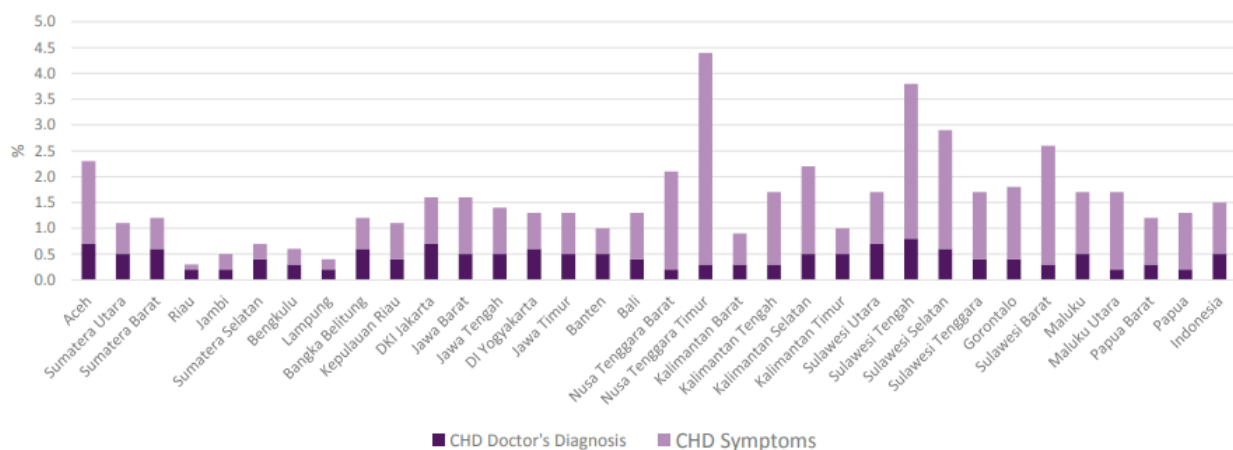
A collection of changes in the coronary arteries, left atrium and left ventricle due to the increase in blood pressure is mainly called as hypertensive heart disease. The function and structure of the myocardium changes due to hypertension that elevates the workload of the heart. This increases the risk of peripheral arterial disease and coronary artery disease, as hypertension severs the endothelial system. Hypertension also increases the risk of heart failure by inducing hypertrophy of the left ventricle (Tackling & Borhade, 2020). Hypertensive heart disease is further classified with the absence or the presence of heart failure where intensive directed therapy is required for patients with the presence of heart failure.

In 2017, the American Heart Association (AHA) and American Cardiology Association (ACA) stated that hypertensive heart disease yields from chronic high blood pressure. Hypertension is defined as diastolic blood pressure higher than 80 mmHg or systolic blood pressure more than 120 mmHg. The baseline for blood pressure is 115/75. The risk of cardiovascular fatality increases for every 10 mmHg diastolic pressure and 20 mmHg for systolic pressure increase (Tackling & Borhade, 2020). One-fourth of all heart failure cases is caused by hypertensive heart disease. The Framingham Heart Study confirms that for specific age and risk factor, the likelihood of heart failure in men increased by 2-fold due to hypertension while for women increased by 3-fold. The development of heart failure is reduced by 64% through proper management of hypertension (Tackling & Borhade, 2020).

The most common form of heart disease is coronary artery disease (CAD). In CAD, atheromatous plaque formation occurs in the blood vessels supplying nutrients and oxygen to the heart. A range of clinical disorders from stable angina, asymptomatic atherosclerosis and acute coronary syndrome such as unstable angina, are used to describe CAD (Regmi & Siccardi, 2020). The symptoms of CAD ranges from chest pain to shortness of breath. The chest pain goes with the name of angina which is usually

accompanied by the feeling of anxiety or constriction and the pain may spread to the jaw, back of the neck, upper abdomen and the arms. Physical exertion usually triggers these symptoms as there is an increase in oxygen demand by the heart muscle.

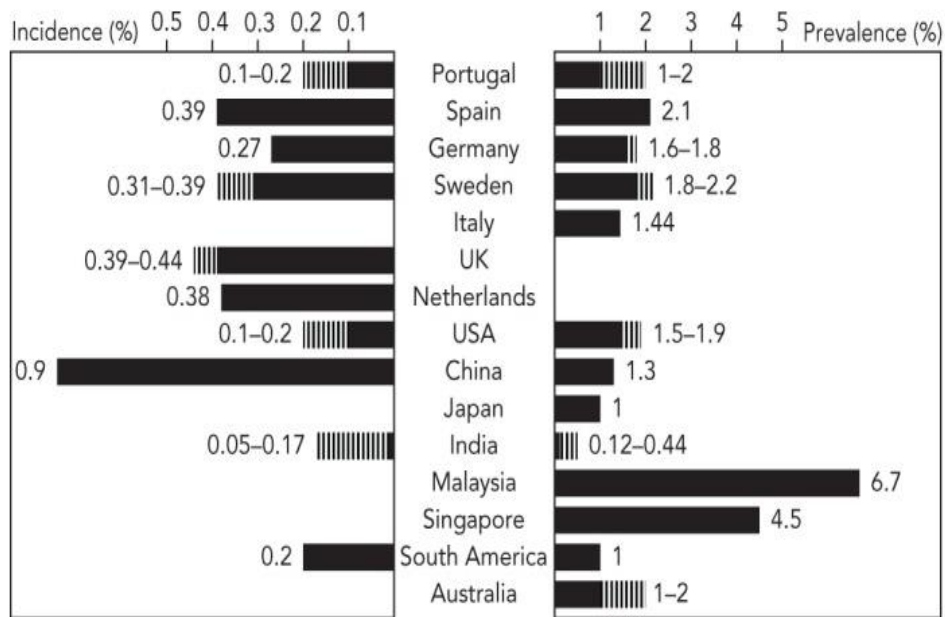
The (AHA), estimated that 16.5 million people older than 20 years old had CAD in the United States, and 55% of them are males in 2018. The trend of CAD in developing countries is worse with increasing mortality. In 2016, the World Health Organization (WHO), declared that CAD was responsible for over 9 million deaths making CAD the leading cause of death worldwide. In Indonesia, in 2012, the second leading cause of death estimated up to 138,400 people or around 9% was CAD. According to Indonesian Mortality Registration System Strengthening Project (IMRSSP), CAD ranked third in Central Java with a total death of 7% while in the more rural area of Pekalongan, CAD ranked 5<sup>th</sup> with a total death of 6%. The highest proportion of patients diagnosed with CAD was in Central Sulawesi with 0.8%. The lowest proportion of patients diagnosed with CAD were Jambi, Riau, Lampung, North Maluku, Papua and West Nusa Tenggara with 0.2%. East Nusa Tenggara was reported with the highest level of CAD symptoms with a total of 4.1% and the second highest level of symptoms was Central Sulawesi with a total of 3%.



**Figure 1.** The Symptoms and Doctor's Diagnosis of Coronary Artery Disease in Indonesia (taken from Conroy, 2017).

Heart failure is any result from functional or structural disorder which impairs the ability to fill the ventricle or eject the blood to the rest of the body (Malik, Brito & Chhabra, 2019). It can be caused by other factors such as, pericardium, myocardium, endocardium, heart valves, heart vessels and metabolic disorder. Heart failure patients mainly have symptoms of impaired function to the left ventricular myocardial. The symptoms that heart failure patients experienced are fatigue during exercise, dyspnea, fluid retention by peripheral and pulmonary edema (Malik, Brito & Chhabra, 2019). Heart failure is mainly classified into three types, heart failure with reduced ejection fraction known as HFrEF, heart failure with preserved ejection fraction known as HFpEF and heart failure with mid-range ejection fraction known as HRmrEF (Savarese & Lund, 2017).

Heart failure affects around 26 million people around the world. In 2012, heart failure was responsible for around \$31 billion; worth 10% more than the total health expenditure in the United States for cardiovascular disease (Savarese & Lund, 2017). The projection of heart failure is even more alarming, there will be an increase of total health cost between 2012 and 2030 by 127%. In the United States, there are currently 5.7 million people suffering from heart failure. Epidemiology studies showed that the risk of heart failure was higher in black men with an incidence rate of 1000 people/year compared to the whites. Heart failure cases was lower in non-Hispanic white males and females by 2.7% and 1.8% compared to non-Hispanic black males and females by 4.5% and 3.8% (Malik, Brito & Chhabra, 2019)



**Figure 2.** The Incidence and Prevalence of Heart Failure Worldwide (taken from Savarese & Lund, 2017)

In 2013, the prevalence of heart failure in Indonesia was 0.13% or approximately 229,696 people. Doctors diagnosed that people suffering from heart failure symptoms were 0.5% or approximately around 530,068 people (Kementerian Kesehatan RI, 2014). According to doctors' diagnosis, it is estimated that the highest number of patients suffering from heart failure is in West Java Province with a total number of 96,487 people around (0.3%) followed by East Java Province with a total of 54,826 people around (0.19%). The area which has the least number of patients is North Maluku Province with a total number of 144 people around (0.02%) followed by Bangka Belitung Province with a total number of 945 patients around (0.1%) (Kementerian Kesehatan RI, 2014).

No	Provinsi	% Diagnosis Dokter (D)	% Diagno- sis/Gejala (D/G)	Estimasi Jumlah Abso- lut (D)	Estimasi Jumlah Absolut (D/G)
1	Aceh	0,10	0,3	3.177	9.531
2	Sumatera Utara	0,13	0,3	11.622	26.819
3	Sumatera Barat	0,13	0,3	4.456	10.283
4	Riau	0,12	0,2	4.929	8.214
5	Jambi	0,04	0,1	925	2.313
6	Sumatera Selatan	0,07	0,2	3.836	10.959
7	Bengkulu	0,10	0,1	1.249	1.249
8	Lampung	0,08	0,1	4.448	5.560
9	Kep. Bangka Belitung	0,05	0,1	472	945
10	Kep. Riau	0,17	0,3	2.327	4.107
11	DKI Jakarta	0,15	0,3	11.414	22.828
12	Jawa Barat	0,14	0,3	45.027	96.487
13	Jawa Tengah	0,18	0,3	43.361	72.268
14	DI Yogyakarta	0,25	0,4	6.943	11.109
15	Jawa Timur	0,19	0,3	54.826	86.568
16	Banten	0,09	0,2	7.267	16.148
17	Bali	0,13	0,3	3.988	9.204
18	Nusa Tenggara Barat	0,04	0,2	1.281	6.405
19	Nusa Tenggara Timur	0,10	0,8	3.117	24.933
20	Kalimantan Barat	0,08	0,2	2.458	6.145
21	Kalimantan Tengah	0,07	0,2	1.126	3.216
22	Kalimantan Selatan	0,06	0,3	1.633	8.167
23	Kalimantan Timur	0,08	0,1	2.203	2.753
24	Sulawesi Utara	0,14	0,4	2.378	6.795
25	Sulawesi Tengah	0,12	0,7	2.233	13.027
26	Sulawesi Selatan	0,07	0,5	4.017	28.695
27	Sulawesi Tenggara	0,04	0,2	616	3.079
28	Gorontalo	0,06	0,2	453	1.509
29	Sulawesi Barat	0,07	0,3	560	2.402
30	Maluku	0,09	0,4	956	4.247
31	Maluku Utara	0,02	0,2	144	1.436
32	Papua Barat	0,08	0,2	446	1.115
33	Papua	0,07	0,5	1.504	10.745
	<b>INDONESIA</b>	<b>0,13</b>	<b>0,3</b>	<b>229.696</b>	<b>530.068</b>

**Figure 3.** Number of patients suffering from Heart Failure in Indonesia (taken from Kementerian Kesehatan RI, 2014)

SGLT2 inhibitor, also known as sodium-glucose cotransporter 2, is the newest antihyperglycemic drug available in the market (Pittampalli *et al.*, 2018). The examples of these drugs are dapagliflozin, canagliflozin, tofogliflozin, ipragliflozin and empagliflozin. The drugs which are approved by the US Food and Drug Administration are empagliflozin, dapagliflozin and canagliflozin. These drugs enhance glycosuria in the kidney and increase sugar excretion from the body. These SGLT2 inhibitor drugs give antidiabetic effectiveness by decreasing vascular pathology and ease normoglycemia (Pittampalli *et al.*, 2018). Research studies showed that treatment using dapagliflozin reduces the systolic blood pressure and cholesterol levels. The SGLT2 inhibitor acts on SGLT2 proteins present in the kidney, it decreases tubulointerstitial burden and decreases the renal nerve tone. The brain senses the decrease in nerve tone signals and decreases sympathetic outflow to vessels. As a result, the blood vessels prevent