Animal Model and Recent Advancement in Cardiac Disease Treatment: A Review

By

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled "Animal Model and Recent Advancement in Cardiac Disease Treatment: A Review" submitted by Asma Ul Husna Samia (15346029) of Summer 2015 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy on 10th October, 2019.

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Ethics Statement

This study does not involve any kind of animal or human trial.

Abstract

Cardiovascular diseases are one of the most perilous diseases causing death throughout the world. Recent developments in the field of cardiac disease treatment are appearing through advancements in science. Significant progress has been achieved in cardiac disease therapy over the past few years such as development in new cardiac medicine, surgery, cardiac imaging and nuclear machine, cardiac electro pacing, non-invasive cardiac treatment and gene therapy etc. Animals have been emerged in history of mankind for research purpose for thousands of years. Experimental animal study gives important knowledge about cause of disease, pathogenesis, problems associated with a disease and about effectiveness and mechanism of action of different drugs and other substances intended for treatment. Animal models can be managed more efficiently than human model because animal's nutritional and environmental characteristics are well manageable. Animal models such as rat, rabbit, guinea pig, canine and zebra fish models etc. are used in research study.

Keywords: Cardiac disease; Animal model; Electrophysiological measurement; Balloon angioplasty; Cardiomyopathy; Tetralogy of Fallot.

Dedication

Dedicated to the Department of Pharmacy, Brac University.

Acknowledgement

At the beginning, I would like to start by thanking Allah Almighty for His infinite blessings and compassion, my source of strength, understanding and wisdom. All praise to Him for blessing me with the enormous patience, strength, and help needed to finish this project. I am really thankful to some individuals for their continuous oversight and guidance without which it seemed very hard to complete this project. Therefore, I recognize them here in order to express my appreciation.

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List of Acronyms

WHO	World Health Organization
CVD	Cardiovascular Disease
HF	Heart Failure
NCDs	Non-Communicable Diseases
GBD	Global Burden of Disease
CABG	Coronary Artery Bypass Grafting
CHD	Coronary Heart Disease
PDA	Patent Ductus Arteriosus Surgery
RTOF	Repaired Tetralogy of Fallot
ASD	Atrial Septal Defect
CS	Coronary Stenting
RFCA	Radio Frequency Catheter Ablation
SE	Stress Echocardiography
TEE	Transesophageal Echocardiography
CREAMS	Cardiac Stereotactic Electrophysiology Epicardial Mapping System
HFD	High Fat Diet
OCT	Optical Coherence Tomography

Chapter 1

Introduction

1.1 Cardiovascular disease

Heart and blood vessels are the composition of cardiovascular system (Olvera Lopez & Jan, 2019). Cardiovascular system is also known for circulatory system. The disease associated with heart and blood vessel are called the cardiovascular disease (CVD). Heart is a core organ of the body as it is associated with blood supply, carriage of oxygen (O_2) and fundamental elements throughout the body. Therefore, lives can be affected if any damage has been occurred to heart (Abd, Abd, & Raman, 2019). Cardiovascular disease is a sober health problem among the universe as it has achieved the title of being number one root for morbidity and fatality (Islam et al., 2016).

1.2 Types of heart disease

Coronary artery disease: Blood supply to arteries becomes indurated because of narrowed heart muscle. Therefore, it causes coronary artery disease (CAD). In developed nations as well as developing nations, CAD has elevated rate of morbidity and mortality. In order to minimize acute cardiovascular events and improve the conditions associated with CAD, an early successful treatment is fundamental (Wu et al., 2019).

Cardiomegaly: People are dying of cardiac diseases and the rate of cardiac death is increasing so fast due to one of a reason called "cardiomegaly". Cardiomegaly is a condition in which heart valves get thickened. And once this occurs, heart finds difficult to process and deliver blood to various parts of body. This can affect any person of any age. Routine medical checkup can surely assist to detect cardiomegaly (Doppala et al., 2019).

Heart attack: Heart attack is now the most prominent cardiovascular diseases among the other CVDs. Heart attack is sometimes lethal coronary thrombosis that basically destroys some portion of heart muscle and it occurs all on a sudden. Albeit heart attack browbeats life, it has some quick signs and manifestations which can assist to save many lives and prevent risks if it has been verified and notified to medical facilities in a timely way (M. E. H. Chowdhury et al., 2019).

Irregular heart rhythm or arrhythmia: Cardiac arrhythmia is induced by alterations in the heart's synchronized electrical activity and is certainly become the base of unexpected mortality within modern era. Arrhythmias are of two types such as impulse production abnormalities and impaired conduction (De Menezes-Filho et al., 2019).

Hypertension: Hypertension means elevated blood pressure. Hypertension has become a most popular chronic diseases and perhaps one of the most important health topics in both developed and developing countries resulting in death as a sole issue. The main cause has not been identified in most hypertension scenarios, and these situations are described as essential hypertension. Hypertension is also described as silent killer disease (Buang et al., 2019).

Congenital heart disease: The most prevalent hereditary malformation discovered in infants is congenital heart disease (CHD). Though new advance in surgery and healthcare management of CHD has a very successful report, some patient face cardiovascular disturbance in their later life (T. Wang et al., 2019).

Myocardial ischemia: Ischemic heart disease means blood supply reduction to the heart. Myocardial ischemia is a pathophysiological multifactorial disorder causing a complicated and explicit relationship within coronary and myocardial vessels. It signifies an in-coordination among the delivery and need of myocardial oxygen that may happen in distinct circumstances. Myocardial ischemia is regarded as the basis of coronary artery disease (CAD) patients ' therapy (Rezende et al., 2019).

Atrial fibrillation: The most significant cardiac rhythm interruption influencing the people is atrial fibrillation (AF). It is a serious burden of disease in the population. Atrial fibrillation increases the incidence of stroke, heart attack and ischemia etc. (Zathar et al., 2019).

Heart valve disease: Alarmingly, heart valve disease is a manifested and significant cause of morbidity and early death in all nations (Draper et al., 2018). Heart valve disease is a lifelong condition and if not treated well, it may become unpreventable and deadly.

Cardiomyopathy: Cardiomyopathy is termed as a set of heterogeneous heart diseases which mostly hinder systolic and diastolic role and therefore can cause long-lasting heart failure as well as swift heart expiry. With elevated morbidity and mortality rates, cardiomyopathy has become frequent common in the people and it leads to approximately 20% of sudden cardiac fatalities in younger people (Li et al., 2019).

Innocent heart murmurs: Innocent heart murmurs is a benign biological phenomenon which is linked to the flow through cardiac structures. It must be separated from pathological auscultatory murmurs, which is the signals of fundamental heart defects. Innocent heart murmurings can develop physiologically in some kids, depending on their size, age and hemodynamic condition at the moment of the evaluation (Ferrara et al., 2019).

Atherosclerosis: Atherosclerosis is the pathogenic method that can possibly trigger disease in the arteries and aorta as a result of reduced or absent blood flow from blood vessel stenosis (Olvera Lopez & Jan, 2019).

1.3 Underlying causes and risk factors of cardiac disease

1.3.1 Causes

There are various causes of developing cardiac diseases. Some of them are given below:

- **Obesity:** Obesity is an increasing global major health issue. It increases the risk of cardiovascular disease. Obesity maintains a noteworthy part in causing atherosclerosis and in adding coronary artery disease. It leads to heart failure by causing functional and structural heart modifications (Csige et al., 2018).
- **Diabetes mellitus:** Diabetes mellitus (DM) contributes as a significant cause for cardiovascular disease (CVD) growth and it ultimately results in death. 44% cardiovascular death are occurring because of type 1 DM and 52% for type 2 DM (Glovaci, Fan, & Wong, 2019).
- **Alcohol consumption:** Alcoholic cardiomyopathy (ACM) is a heart disease and it is triggered by the consumption of chronic alcohol. Chronic alcohol consumption is also a reason of myocardial dysfunction (Shaaban & Vindhyal, 2019).
- **Hormones:** Cardiovascular disease increases with lower estrogen level in females. Also, lower testosterone and estradiol levels in male develop coronary artery disease (Osadnik et al., 2019).
- **Tobacco smoking:** Tobacco smoking is a chief reason of illness and fatality in cardiovascular disease (CVD). CVD dangers associated with smoking are maximum in present and newest smokers, comparing with the people who have not smoked or those who have stopped smoking in the past (Banks et al., 2019).
- **Age and gender:** Before age 55, the incidence of occurring cardiovascular disease in females is not higher. But at the age of 55, both men and women, suffer from lifetime risk of developing cardiovascular death. Moreover, women have more advanced

chance of anguishing heart failure, on the other hand, men have higher likelihood of emerging coronary artery disease (Osadnik et al., 2019).

1.3.2 Risk factors

Early diagnosis is a must for treating cardiovascular disease and making life better (Wu et al., 2019). The development of risk of cardiovascular diseases are associated with numerous factors. Some aspects such as always eating fried oily food, physical inactivity or no regular exercise, no eating fruits, eating red meats in every week, people of elderly age and passive smoker are categorized as risk factors of developing cardiovascular disease (Abd et al., 2019).

1.4 Cardiac death rate

Cardiovascular diseases (CVD) are a significant contributor to worldwide fatalities in modern countries and are increasing in incidence in developing nations as well as posing a significant health industry challenge. Worldwide, 85% of all disorders are reported because of CVDs (Jawad Hashim et al., 2018)

1.4.1 Perspective of international countries

A total of 840,768 deaths (635,260 cardiac) have been occurred in United States in 2016 due to cardiovascular disease. In 2019, approximately 1,055,000 people, including 720,000 latest and 335,000 periodic coronary incidents, are anticipated to experience coronary incidents. Approximately 6.2 million American adults were reported of having heart failure (HF) between the year of 2013 & 2016. In the date of April 27, 2018, approximately 3,994 Americans were listed for heart transplant (Benjamin et al., 2019).

As per World Health Organization (WHO), death rate due to cardiac disease has attained 18.50% in 2017 in Iraq. In 2019, approximately 65% people are reported of having hypertension, 64.4% people having circulatory heart diseases, 46.3% people have family history of cardiac disease (Abd et al., 2019).

Indian ischemic heart disease incidence is 37 per 1000 residents. In India, early cardiac death has increased by 59%, from 23.2 million to 37 million between the year of 1990 and 2010. Among the rural region of India, coronary heart disease has exceeded 40% in men and 56% in women between the year of 2000 and 2015 (Pattnayak et al., 2019).

The British Heart Foundation (BHF) stated on May 13 that there is an unusual rise in heart deaths in the folks of 75 years old and adult which is a drastic rise in half a century. Approximately, 42384 people died in 2017 compared to 41042 people died in 2014 (The Lancet, 2019).

1.4.2 Perspective of Bangladesh

Cardiovascular disease (CVD) is a significant challenge for Bangladesh's healthcare industry. Bangladesh has the greatest incidence of CVD risk factors among South Asian nations. 99.6% of men and 97.9% of women in Bangladesh are subjected to minimum one defined risk factor of CVD. In terms of age, people who are 35 years of old or above have 1.8% chance of having stroke and 3.8% of suffering from heart diseases (Jawad Hashim et al., 2018).

1.5 Rationality of using animal model for scientific purpose

From ancient period animals were used in research area for scientific purpose. In ancient Greece, to develop the knowledge of living animal, Aristotle examined animals in his experiment. To define human anatomy, physiology, pathology and pharmacology, animal study is always helpful and knowledgeable (Andersen & Winter, 2019). Again, animal

Figure 1: Schematic featuring the use as models for biomedical research of cattle, pigs, sheep, and chickens

(Hamernik, 2019)

representations are crucial for assessing the living importance of *in vitro* results and also aimed to create relationships between origin and consequence that are typically correlative to clinical observations. Relationships between cause and effect can be evaluated in animal models in a definitive manner but are hard to demonstrate in human research. Furthermore, the findings of animal studies provide original data on the safety and potential effectiveness of new therapeutic combinations which is not possible in human body (Hajishengallis et al., 2015).

Chapter 2

Methodology

2.1 Animal model

A model is a replica or artificial or actual imitation object which hermetically represents similarity or illustration of another thing or another individual (*Selection of Biomedical Animal Models*, 2008). Animals are helpful in research study to establish medical treatment, to evaluate the toxicity or poisonous level of the medicine, to verify the wellbeing and worth of medicinal product envisioned for humanoid benefits as well as other purposes like business, health services and biomedicine etc. Research study has been carried out on living creatures from 500 BC (Ch, 2016). Human co-operation on research is less in number than animal. Animal models of shortfalls in human behavior require undertaking animal experiments in the expectation of acquiring latest information that can be utilized in human beings. (Sjoberg, 2017). In addition, in the research of human illnesses, laboratory animal models play prominent role. But sometimes the use of suitable animal relics not only dismissive for primary enquiry but correspondingly for the advancement of analytical and healing instruments (Fan et al., 2016). The disease which to be examined is created artificially in animals. In laboratory the diseases are generated artificially to imitate the human disease (Ch, 2016). In some diseases like cardiovascular disease because of the system's biological complexity, the animal model is an emergence pre-clinical focus to boost the understanding of cardiovascular disease and discover new drugs to remedy the impaired heart (Camacho et al., 2016). The value of animal model is not only that it helps in terms of human but also in terms of animal itself because there are many human diseases which sometimes threaten the animals (Barré-Sinoussi & Montagutelli, 2015).

2.2 Selection criteria for an adequate animal model

Researchers are trying to stir up comparable elements of the ailment in creatures to produce an animal template of the disease of similar type for practically every possible human disease. Animals, allegedly predictive, "are used to detect and quantify the effect of a therapy, whether to heal an ailment or to evaluate the deadliness of a toxic substance"(Ch, 2016). The choice of any model for studies, but especially animal models, should be centered on certain criteria such as adequacy as an analog, content transferability, species genetic consistency where appropriate, output of generalizability, background understanding of biological characteristics, price and accessibility, laboratory interference's flexibility and robustness, ecological impact and significance of ethics. The choice or refusal requirements for specific animal models also include usual customer's work inside a specific system, jeopardized outcome of subsistent illness or circumstance, the current body of understanding on the issue being addressed and particular characteristics of the animal, such as distinctive replication or microflora, that can vacillate a specific animal valuable. Furthermore, feasibility and link between human and drug safety are some other requirements of animals for biomedical research (Leong et al., 2015). Moreover, the chief area of establishing animal template for enquiry stands to conduct a study in which human circumstances are as efficiently as conceivable phenocopied in the experimental animal (Esteves et al., 2019). However, the right choice of the disease like cardiovascular animal model is a major challenge (Santos et al., 2015).

2.3 The 3Rs in animal model

The 3Rs basically stands for replacement, reduction and refinement. Replacement is a procedure of replacing animals with any human donor or math and computer models or tissues and cells. Reduction is a technique of reducing number of animals by obtaining enough data from fewer animals or by acquiring enough details within same number of animals. Refinement means mitigation of animal pain, misery, discomfort or permanent damage and enhance animal welfare (Graham & Prescott, 2015).

2.4 Types of animal models used in research study

The most humane treatment of research animals is a requirement for effective animal studies, apart from being a barrier (Cheluvappa et al., 2017). Many different types of animals are used for research purpose. Depending on the research purpose animals may vary. Animal usage has increased from previous. Numerous animals have been used in different research works since many years. Their numbers according to years are given below in a table:

Table 1: Animals Used in Research

Animals	2017	2016	2015	2014	2013
Cats	19,368	20,193	21,081	22,398	25,815
Dogs	74,853	66,763	67,181	65,153	74,077
Guinea Pigs	206,174	203,161	186,897	186,457	211,495
Hamsters	103,223	106,828	106,729	144,377	143,679
Rabbits	162,687	139,391	154,010	170,917	190,068
Non-human primates	110,194	109,821	105,584	105,665	107,256
Pigs	57,589	56,059	52,131	50,609	61,624
Sheep	15,848	13,305	12,042	12,265	13,424
Other farm animals	26,213	23,216	32,205	33,576	39,899
Other animals	156,805	202,840	166,287	209,310	171,639
Totals	932,954	958,256	904,147	1,000,727	1,038,976

2.4.1 Chimpanzee model

Chimpanzees have been the only large, non-human species used in biomedical research, mostly as tools for studying behavior patterns and cognitive skills. The use of chimpanzees to study human illnesses is scientifically rigorous and is often relied on genetic connection between the species recorded between 98 and 99 percent (Bailey & Bailey, 2011). Human and chimpanzee genetical relations actually lead to cross-species disease propagation as well as habitual interactions (Negrey et al., 2019).

2.4.2 Mice model

The mouse has evolved into the leading mammalian model tool for study goal over the previous era. Scientists across a broad spectrum of biomedical areas inclined to the mouse due to their similar genetic and physiological familiarity with humans and the comfort to which their genome can mostly be modified and evaluated. Mouse model for cardiovascular disease has given useful information into systems that emerge throughout cardiac aging process and in reaction to a multitude of pathologies (Lindsey et al., 2019). Nearly all mice's genes share features that are similar with the human genes. The usage of mice as model frame for the research of human physiology is based on the species ' genetical and physiological harmonies (Perlman, 2016).

2.4.3 Rat model

The first explicitly domesticated mammalian species were rats to be conducted in the labs. Scientists used the brown Rattus norvegicus two centuries earlier to comprehend physiology and medicine in human beings. Rats represent a significant model for researching the processes of disease and discovering, affirming and experimenting with new compounds to enhance human health (Shimoyama et al., 2017). The rat has more benefits than mouse and other species to study human disease (Iannaccone & Jacob, 2009).

2.4.4 Rabbit model

While genetically engineered mice play a key role in research study, rabbits are helpful animal models for ascribing animal models to humans. (Shiomi, 2009). The rabbit was used in multiple immunological research as the first animal model and that was vital, for instance, for rabies vaccine growth by Louis Pasteur in 1881 (Esteves et al., 2019). Rabbits are comparatively cheap to buy, maintain and keep compared to bigger models of animals. They are simple to grow and manage and are a excellently-established model for the science and regulatory groups to recognize (*Kingfisher Biotech Circular Subject : Rabbit as an Animal Model*). The rabbit is a secure model of human disease and a medically appropriate version. In terms of airway structure and reactions to inflammatory intercessor, the characteristics among rabbits and humans show the importance of this animal in disease research (Kamaruzaman et al., 2013).

2.4.5 Guinea Pigs model

The terms ' guinea pig ' are associated with scientific investigation and therefore this animal model was the first to be used in the research of communicable diseases for probably 200 years (Padilla-carlin et al., 2008). Due to the commonalities between organ extent, coronary physiology, immunology and human physiology, pigs continues to stand out as the most approachable model for clinical development guidelines (Camacho et al., 2016).

2.4.6 Dog model

Researchers used comprehensive animals in experiments for perceiving the organic as well as environmental conditions by controlling anility, hindrance and endurance. Indeed widely researched mammals such as rats and mice may never demonstrate comparable environmental circumstances with humans whom are subjected, the companion dog is currently suggested as an important model for actually knowing human hereditary and ecological subsets of illness along with fatality (Hoffman et al., 2018). The relevance of animal emotive illnesses, particularly dogs, has been used to understand human diseases ' genetics and pathogenesis and to develop new medical therapies (Monath, 2012). In some dog territories, selective geniture and adaptive selection of specific characteristics have inadvertently maintained harmful disease-associated genetic variants (Shaffer, 2019).

2.4.7 Zebrafish model

Zebrafish may explicate cardiovascular pathophysiology because of the preservation of genes as well as developmental processes, comparable heart rate as well as cardiac anatomy and activity. Zebrafish (*Danio rerio*) has appeared in recent decades as a useful model for vertebrates to study cardiovascular progression (Giardoglou & Beis, 2019). The zebrafish template has been used for centuries to study evolution and pathophysiology and contains a primarily maintained physiology as well as morphology with mammals that enable for a broad spectrum of genetic alterations, along with the recent methods to genome engineering (Gut et al., 2019). Therefore, zebrafish shows an amazing regenerative ability, hoping to manifest humans (Gut et al., 2019).

2.4.8 Non-human primates

Designs of non-human primates are identical with human physiology, metabolic, biochemical and genetic (Camacho et al., 2016).

2.5 Drawbacks of Animal Model

Defenders of some kind of animal experimentation, along with animal welfare extremist groups and anti-vivisectionist organizations, think that animal testing are brutal and needless, irrespective of their intent or advantage. More usually, the bioscience society acknowledges that only through an ethical system animals may be used for studies (Festing & Wilkinson, 2007). Animal need in experiments and education throughout the developed countries are answerable to rigorous ethical rules. Rate of change in laboratory animal selection decreases study's detection range and improves the amount of animals needed for statistical accuracy (Cheluvappa et al., 2017). Apart from the core ethical considerations, some are fewer drawbacks of animal testing, such as the need for skilled labor, time-consuming procedures and increased costs. The claim is that animals have feeling of pain and distress and therefore animal usage for experiments is ethically wrong and must be discouraged (Doke & Dhawale, 2015). The value of animal model is questionable in anticipating the accuracy of treatment method in clinical trial because animals do not assure the correct information that will occur in mankind (H. Bart van der Worp et al., 2010). After several centuries of human drug discovery, there is still a lack of published, significant, extensive information to confirm animal use in drug development testing and to highlight its probabilistic nature in terms of human safety / poisoning and effectiveness (Bailey & Balls, 2019). Sometimes, animal models struggle to duplicate the nature of human behavioral fluctuations and have restricted capacity to trace certain impacts. Furthermore, some of the outcomes acquired from fundamental (animal) studies throughout the clinical studies are not observed (Andersen & Winter, 2019).

Chapter 3

Recent Advancement in Cardiac disease management

3.1 Treatment methods for cardiac disease

Scientific progress in acknowledging coronary artery disease (CAD) pathophysiology has resulted towards a decline within death towards the move to the 20th century. (Kandaswamy & Zuo, 2018). As per the World Health Organization (WHO) description, cardiovascular diseases are liable to aim at 17.5 million fatalities in the time of 2012 (concurrently 7.4 million and 6.7 million because of stroke and CHD), which accounts for the 31% of all demises globally per year. (Zhao et al., 2017). To manage CVDs correctly, researchers had to examine the variables causing their etiology and either dismantle present pharmaceutical products or establish brand new medicines. Continuous advancement in gene therapy has ultimately made one of the acceptable treatment opportunities for CVDs (Machaj et al., 2019).

3.1.1 Types of treatment

3.1.1.1 Surgery

Coronary Artery Bypass Grafting: Coronary artery bypass grafting (CABG), was first launched in medical exercise in 1964 and then the process has subsequently turned the 'gold standard' aimed for coronary atherosclerosis therapy. The most prevalent and extensively endorsed operation now includes the use of the left inner mammary vein to revascularize the left anterior downward coronary vein as well as solo or even extra vein bypass surgery for some other certain coronaries. It tends to partake a defensive impact arranged for atherosclerosis development (Bargagna et al., 2019).

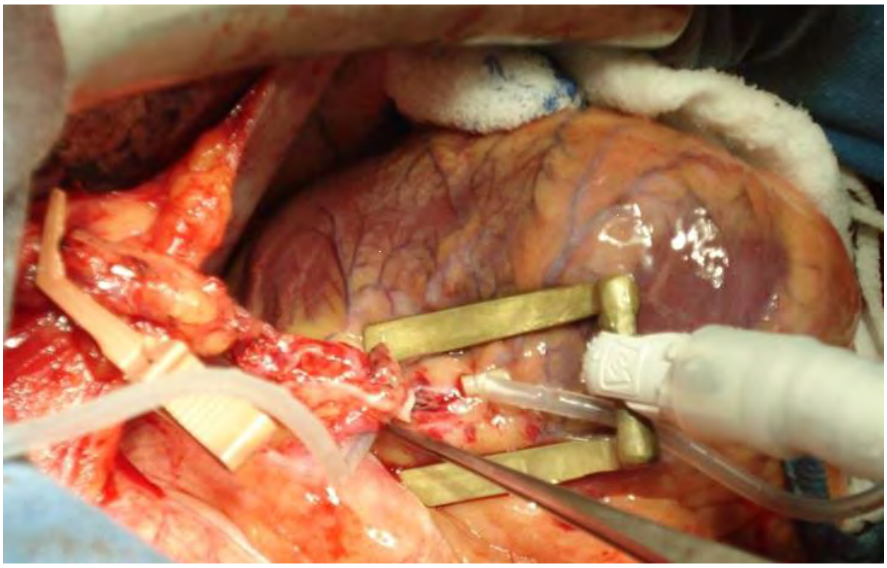

Figure 2: Picture of Coronary Artery Bypass Grafting

Aortic Aneurysm Surgery: Aneurysmal disease from the aortic root can damage any aorta section, to the aortic bifurcation. The therapy of aortic aneurysms has progressed drastically over the last three centuries, with the advent of endovascular aneurysm cure utilizing stent grafts resulting in a significant paradigm change in aortic aneurysm operation. The technical aspects of aortic aneurysm maintenance differ significantly based on where an aneurysm is positioned (Swerdlow et al., 2019).

Figure 3: Picture of Aortic Aneurysm Surgery

Tetralogy of Fallot surgery: This procedure is used to evaluate cardiac defects that is triggered by reduced pulmonary blood circulation. By successfully improving surgical methods and perioperative treatment, a satisfactory 30-year successful survival rate of recovered Fallot tetralogy (rTOF) is accomplished (He et al., 2019).

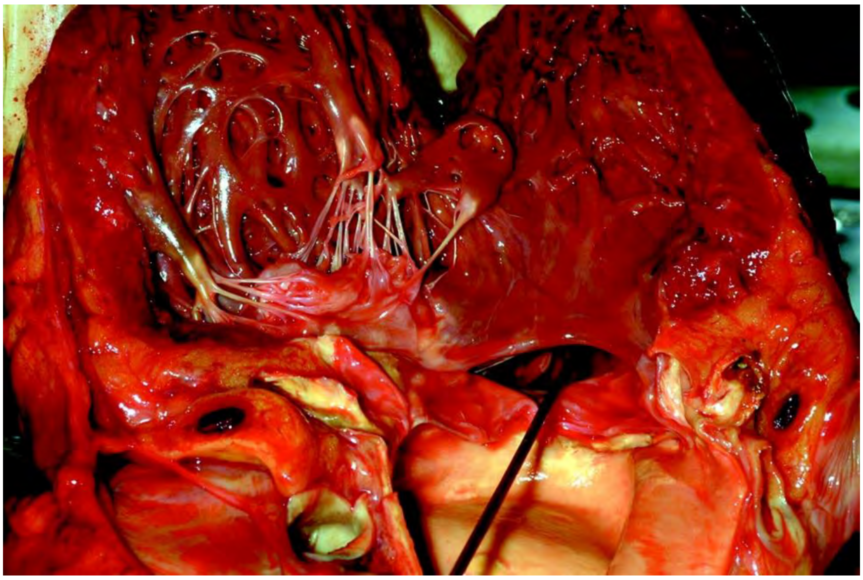

Figure 4: Picture of Tetralogy of Fallot Surgery

Patent ductus arteriosus surgery: Patent ductus arteriosus operation (PDA) is performed with medicinal products, catheter-based techniques and surgery. The objective of the therapy is to close the PDA in order to avoid complexity and recover the impacts of enhanced blood volume. Some standard operating steps helps to correctly perform surgical excision of the patent ductus arteriosus. The anatomical landmarks ' knowledge and simple precautionary measures lead to high degree of indemnity. The surgical ligation method differs with the patient's age (Kariyappa & Kumar, 2019).

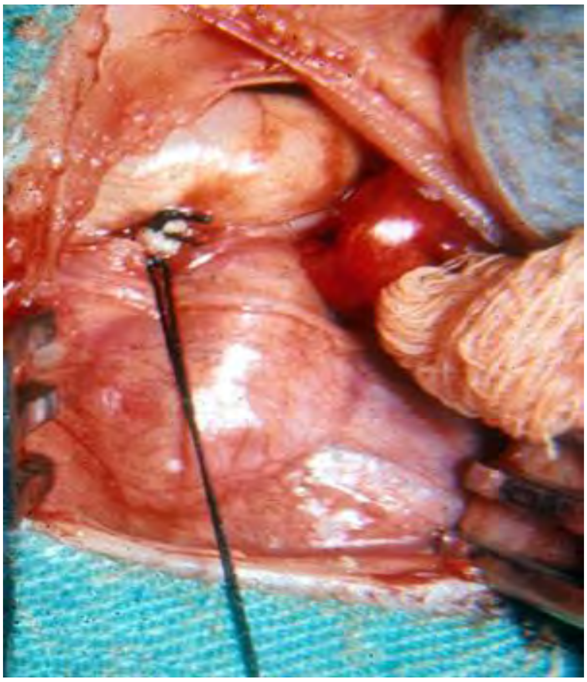

Figure 5: Picture of Patent Ductus Arteriosus Surgery

Atrial septal defect surgery: Robotically aided atrial septal surgery with an endoscopic, closed chest method is a form of finely invasive cardiac surgery conducted on atrial septal deficiency (ASD). Since the last few years, in the cardiac catheterization laboratory, atrial septal defect (ASD) can now be operated. ASD was one of the primary method to be handled in a transcatheter strategy (Boudoulas et al., 2019).

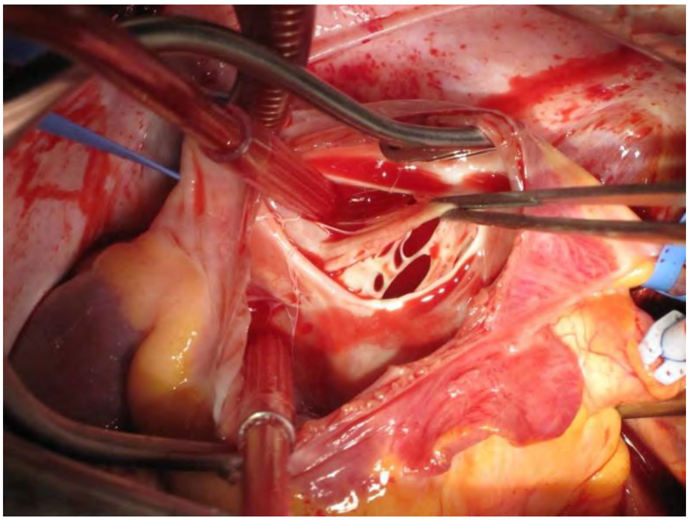

Figure 6: Picture of Atrial Septal Defect Surgery

3.1.2 Cardiac imaging and nuclear medicine

Balloon angioplasty through stenting: Sometimes denoted as under skin transluminal angioplasty, this operation utilizes a balloon-tipped catheter, developed across a thin wire and fed with contrast liquid to force the plaque against the artery wall and extending the opening to boost blood circulation. Many of the new techniques for angioplasty now function with a drug-coated balloon to decrease cell proliferation or restenosis after surgery. Angiography (X-ray screening with contrast medium to demonstrate blood supply) is used to conduct balloon angioplasty. Progressively, balloon angioplasty is often used in combination with the other therapies rather than as a stand-alone therapy (Technologies, 2018).

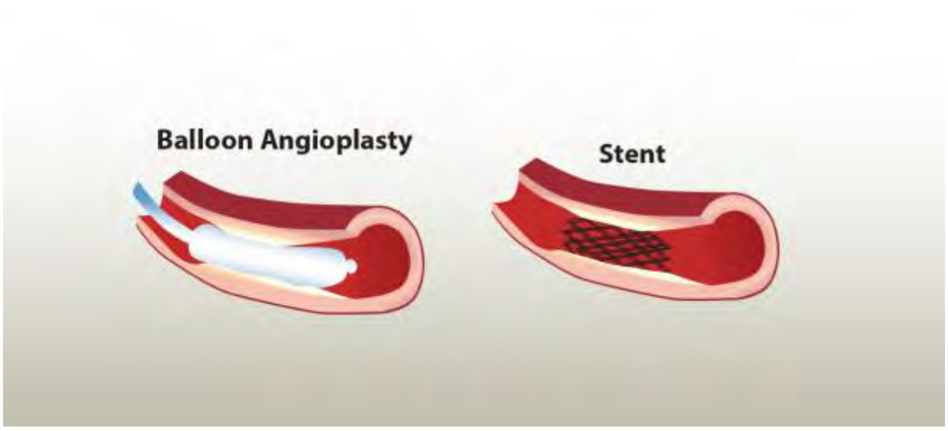

Figure 7: Picture of Balloon Angioplasty with Stenting

Pantheris lumivascular atherectomy system: This is a selective atherectomy scheme with a tomography of optical consistency. Optical consistency tomography is a technology of imaging (now a days used in eye observation) that utilizes light to provide visual guidance in three dimensions throughout the operation. The presently authorized fluoroscopy is perquisite for the Pantheris model (Technologies, 2018).

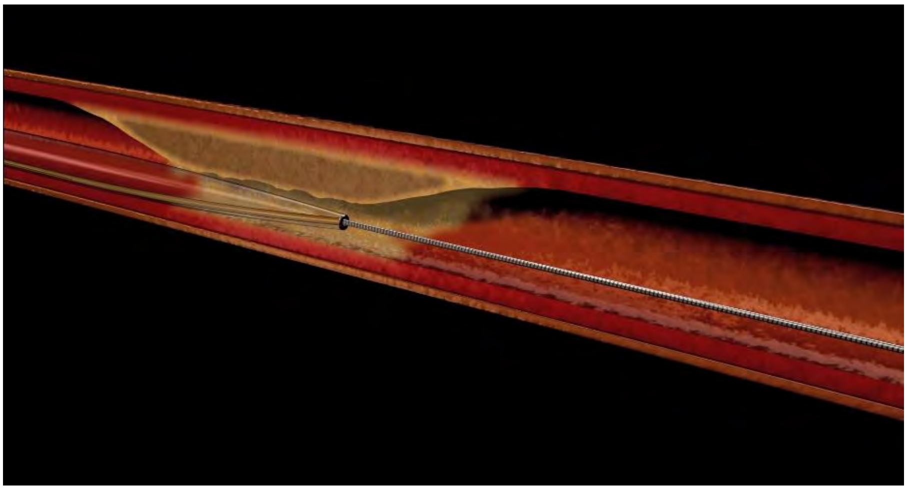

Figure 8: Picture of Pantheris Lumivascular Atherectomy System

Coronary angiography: A coronary angiogram is a method of utilizing X-ray imaging or radiography to observe the blood vessels of the heart. Coronary angiography is being operated to check the condition of an coronary artery misaligned or transplant circumvent and also to acquire an opportunity aimed to get urgent intervention treatment, as well as to minimize additional costs for the medical system (Rupprecht et al., 2019).

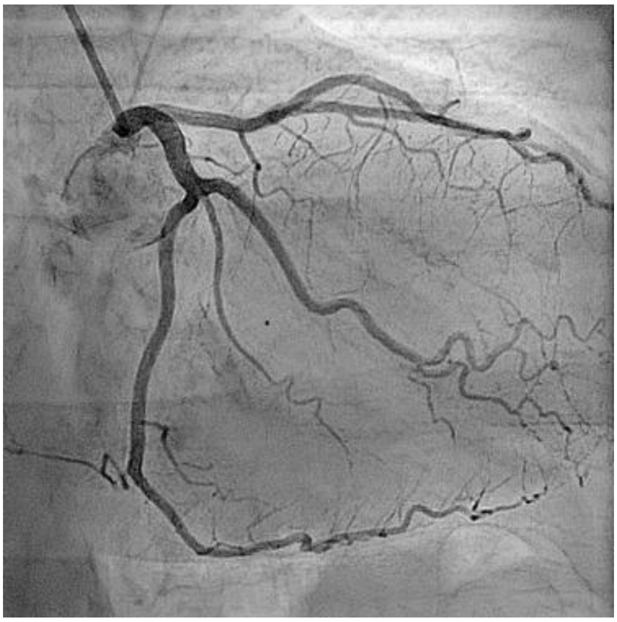

Figure 9:Picture of Coronary Angiography

Ventriculography: Throughout the last generation, catheter-based ventriculography has developed and has already been substituted in many cases by cardiac ultrasound. Ventricular activity despite of changing continues a significant component of the evaluation of myocardial dysfunction and prognosis. Ventriculography can further assess left ventricle (LV) function characteristics (Innovations & Conti, 2019).

Figure 10: Picture of Ventriculography

Coronary Stenting: Coronary stents (CS) are extensible metallic tubular instruments which are brought into the coronary arteries showing stenosis owing to an inherent atherosclerosis disease. In 1980s, the coronary stent was first introduced and outstretched to develop in aspects of its form, composition and material that were incorporated into them (Chhabra et al., 2019).

Figure 11: Picture of Coronary Stenting

3.1.3 Cardiac electro pacing

Cardiac electrophysiology studies: Cardiac electrophysiology is the study of heart electrical function elucidation, diagnosis and treatment. There has been many developments in fundamental cardiac electrophysiology from the use of genetic instruments to a greater knowledge of electrophysiological dysfunction (Hussein et al., 2019).

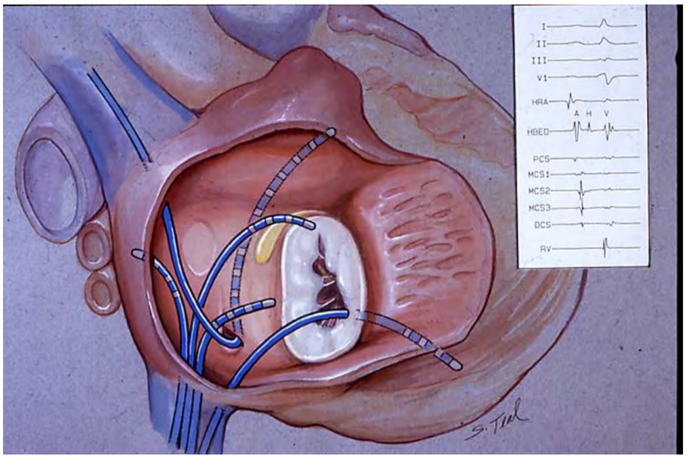

Figure 12: Picture of Cardiac Electrophysiology

Radio frequency catheter ablation: Catheter ablation is a method that utilizes radiofrequency force to ravage a tiny region of cardiac tissue that causes fast and irregular or uneven heartbeats Atrial fibrillation (AF) is a significant global health threat until radiofrequency catheter ablation (RFCA) has been established by Haissaguerre (French cardiac electrophysiologist) and his collaborators. RFCA is suggested for symptomatic and antiarrhythmic medications after 20 years of its implementation (Kim et al., 2019).

Pacemakers & implantation: In recent years, pacemaker installation rates have risen enormously, particularly among the elderly. The development of the population, the new technological advancements of these machines and the increasing number of clinical signs are the primary reason for rising the rate. Approximately 1.25 million permanent pacemakers are predicted to be implanted globally each year. (Reyes et al., 2019).

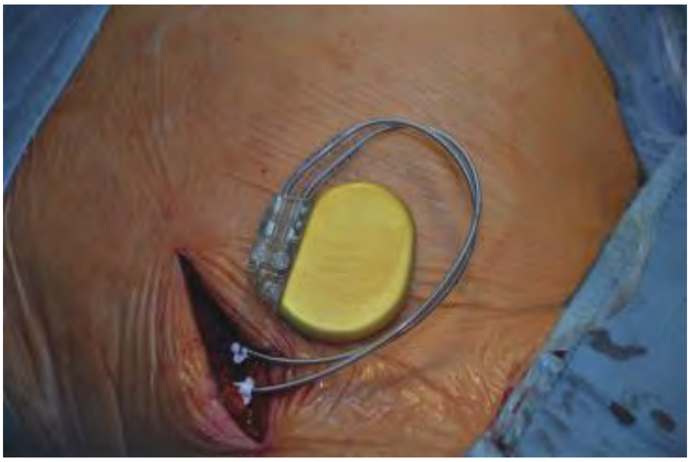

Figure 13: Picture of Pacemakers & Implantation

3.1.4 Non-Invasive Cardiac Treatments

Holter TMT: In 1957, Dr. Norman J. Holter and his team built "Holter monitor" which is an outpatient electrocardiographic device. The Holter monitor is a system that operates on the principle of Galvanometer (principle of conversion of electrical energy into mechanical energy) to record an individual's electrocardiographic readings (Mubarik et al., 2019).

Stress echocardiography: Stress echocardiography (SE) is referred to a well-developed non-invasive method most commonly used during coronary artery disease (CAD) diagnosis. It was mainly utilized for the diagnosis and analysis of patients suffering from chest pain who have the chance of intermediately occurrence of coronary artery disease (Steeds et al., 2019).

Figure 14: Picture of Stress Echocardiography Room

Transesophageal echocardiography: Transesophageal echocardiography (TEE) is a secure and minimally invasive method which can provide anatomical and hemodynamic data of good quality regularly (Jaidka et al., 2019).

Figure 15: Picture of Transesophageal Echocardiography

Doppler echocardiography: It is a successful method for cardiac purpose activity evaluation. The method allows blood velocity measurements across blood vessels, heart valves and heart chambers and afterwards these are benefited for detecting CVDs. Moreover, doppler echocardiography is very helpful for studying disrupted hemodynamics *in vivo* CVD models (Benslimane et al., 2019).

Figure 16: Picture of Doppler Echocardiograph Machine

3.1.5 Gene therapy

Gene therapy is an useful method for the prevention of cardiovascular diseases of inherited and obtained (Rincon et al., 2015). A range of cardiovascular genetic diseases can be cured one day through gene excision innovation. Germline genome excision and modification claims to eliminate inbred cardiovascular diseases completely since descendants and future generations of impaired families (German et al., 2019). The importance of cardiovascular gene therapy had become obvious in the early 1980s, when endovascular catheter methods showed that direct intra-arterial genetic recombination was feasible (Ylä-Herttuala & Baker, 2017). At present, researchers have evaluated gene therapy's capacity to alter the cardiac genotype of both animal models and left-ventricular (LV) dysfunction patients. (Kieserman et al., 2019). Whereas pharmacological and invasive CVD treatments attain symptom decrease and slow the development of the disease, optional therapeutic methods are still urgently needed to treat CVD and HF efficiently or even to heal them. Progress in molecular cardiology has clarified the molecular alleyways and contributory genetic factor engaged in the introduction as well as development of cardiovascular diseases.

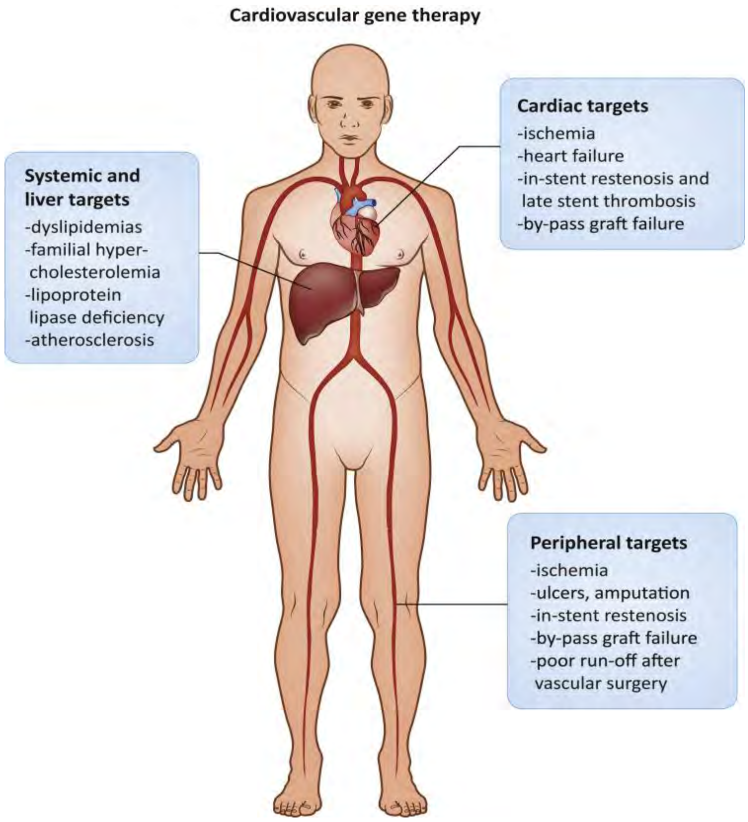

Figure 17: Cardiovascular Gene Therapy (Ylä-Herttuala & Baker, 2017)

These outbound insights present an opportunity for gene therapy to be used as a new method of treatment for CVD and HF (Rincon et al., 2015). Cardiac gene therapy needs to adapt new advancement in vectors, delivery systems, objectives and clinical parameters and is ready for drastic success in the upcoming future (Ishikawa et al., 2018).

Table 2: Techniques used in gene therapy for transmitting CVD treatment (Rincon et al., 2015)

Techniques	Process	Significance	Benefits
Catheter-based anterograde arterial infusion	Intracoronary perfusion, Intracoronary perfusion + Balloon occlusion and Intracoronary perfusion + Balloon occlusion + Venous occlusion	Instable and sophisticated heart failure patients	Straightforward and minimally invasive with heart specificity and uniform distribution
Retrograde intravenous	Intravenous perfusion + Venous occlusion	Patients with decreased circulation of the coronary artery and restricted revascularization capacity	Can attain greater concentrations of cardiomyocyte transduction
Pericardial delivery	Percutaneous approach	Patients that are not appropriate for high levels of circulatory neutralization antibodies	Long-term vector contact may boost transduction concentrations and may be secure and minimally invasive

In the above table, many techniques of gene therapy along with process, significance and benefits are pointed out.

3.1.6 Medicine

Table 3: Cardiac Drug Class and Example

Drug Class	Example	Description	Reference
Calcium channel blocker	Amlodipine	Amlodipine is an oral dihydropyridine with the lengthiest half-life of 30 to 50 hours and was first accepted by the Food and Drug Administration (FDA) in 1987.	(Bulsara & Cassagnol, 2019)
Beta blocker	Metoprolol	Metoprolol is used for chest pain, heart failure, myocardial infarction, atrial fibrillation / flooding, and high blood pressure.	(Morris & Dunham, 2019)
Positive inotropic	Digoxin	Digoxin functions as an atrioventricular nodal blocking substance for the management of atrial tachydysrhythmias in patients suffering from congestive heart failure (CHF) as well as which is a cardiac glycoside. It develops the life quality of patients with CHF.	(Cummings & Swoboda, 2017)
Loop diuretics	Furosemide	The FDA has permitted the use of furosemide as the medication of volume overload and secondary edema conditions to exacerbate congestive heart failure	(Khan & Siddiqui, 2019)
Angiotensin II receptor blocker	Candesartan	For the treatment of high blood pressure and heart failure, candesartan is mostly given as monotherapy.	(Bulsara & Makaryus, 2019)

3.2 Treatment scenario of cardiovascular disease in Bangladesh

Bangladesh has little achievement over the years in managing the increasing burden of diseases that are not conveyed efficiently for instance cardiovascular ailments (Biswas et al., 2017). Excellently-planned, community-based, national survey studies concentrating on heart disease and related jeopardy variables are critical in assessing the seriousness of heart disease incidence throughout Bangladesh, in implementing precautionary approaches to mitigate yet more incidence and decreasing CVD-related morbidity and mortality (M. Z. I. Chowdhury et al., 2018). In 2017, a conference was held on "Cardiology and Cardiac Surgery" at 4th Dhaka Live 2017. There renowned cardiologists from home and abroad, doctors and other healthcare professionals took part and shared updates on heart health. They said all kinds of cardiac disease treatment are possible in the country and meanwhile Labaid hospital as well as many other hospitals at present offers world class cardiac therapy and also Labaid may give treatment to 500 patients in a month ("Cardiac Diseases: World class treatment available at home | The Daily Star," 2017). Hospitals such as Dhaka Medical College Hospital (DMCH), Apollo Hospitals Dhaka (AHD), National Heart Foundation Hospital & Research Institute (NHFH & RI), National Institute of Cardiovascular Diseases (NICD), United Hospital Limited (UHL), Ibrahim Cardiac Hospital and Research Institute, and Islami Bank Central Hospital provide cardiac disease treatment. Cardiovascular drug markets are associated with 55% ARBs and among them 61.67% are losartan, 33.33% are olmesartan, 21.67% are valsartan and irbesartan (1.67%)), 25% ACEIs and among them ramipril (90%), 6.67% are perindopril, 3.33% are captopril and 1.67% are enalapril, 18.33% CCBs and among them 64.41% are bisoprolol, 38.98% are metoprolol, 15.25% are carvedilol, 1.69% are atenolol and 1.69% etc. are propranolol (Shahriar & Islam, 2018).

Table 4: Available cardiac surgery in Bangladesh

Hospital	Surgery	Reference
Apollo Hospitals Dhaka	a) Coronary Artery Bypass Surgery (CABG) b) CABG by beating heart technique c) Emergency and urgent CABG d) Aortic valve replacement e) Valve replacement with left aterioxpexies and maze procedures f) Aneurysm surgery by Bentall procedure	"Cardiothoracic & Vascular Surgery - Apollo Hospitals Dhaka," n.d.
IBN Sina – Trust	a) Echocardiogram b) Duplex study c) Color Doppler d) Holter ECG	"IBN Sina - Trust," n.d.
Ibrahim Cardiac Hospital and Research Institute	a) Coronary Angiogram (CAG) b) Transradial Coronary c) PDA/PA - Stenting (Cocoon) d) Carotid Angioplasty	"Welcome to Ibrahim Cardiac [Hospital & Research Institute]," 2016
Labaid Cardiac Hospital	a) Patent Ductus Arteriosus Ligation b) Ventricular Septal Defect Closure c) Atrial Septal Defect Closure	"Labaid Cardiac Hospital," n.d.
National Heart Foundation of Bangladesh	a) Holter Monitoring b) Cardiac Catheterization c) Intravascular Ultra-sound (IVUS) d) Pediatric Color Doppler Echocardiography	(.:: "Our Services | Welcome to National Heart Foundation of Bangladesh ::.," n.d.)

In the above table, the treatments that are available in Bangladeshi hospitals are pointed out.

Chapter 4

Discussion on recent animal research of cardiac disease

4.1 Animal model of hypertension

Animal models have always been beneficial for uncovering the etiology of hypertension and trying new therapeutic methods of treatment. The effectiveness of animal models relies on their integrity of how they are revealing the various types of human hypertension and also how they helps to understand the pathophysiology, mitigation and diagnosis of high blood pressure, along with therapeutic reactions and the excellence of research in these models (experimental modeling and reproducibility) (Lerman et al., 2019).

4.1.1 The usefulness of silibinin in a rat model of high blood pressure within pulmonary artery

Silibinin is a medicinal plant extracted from Silybum marianum (Cheung et al. 2010). A single subcutaneous injection of monocrotalin triggered pulmonary arterial hypertension (PAH). The rats were kept chronically hypoxic situation (10% O_2) both with and without silibinin. Systolic pressure of right ventricle, Fulton index (quantity proportion of right ventricle divided by left ventricle as well as septum), percent width of the pulmonary boarder and then vascular obstruction points were recorded as well as quantified, to analyze the potency of silibinin on PAH. Therapy with silibinin lowered RVSP and Fulton index by one week. (Zhang et al., 2019).

4.1.2 Exacerbation of atherosclerosis through renovascular high blood pressure in rabbit of cholesterol nourished

Hypertensive rabbit model (HTN) is obtained by withdrawing half ablation of right kidney blood vessel and left kidney surgically. Aortic and then coronary atherosclerosis of hypertensive rabbit model, they are depicted with streamlined rabbits after a 16-week diet of cholesterol. Hypertension did not change plasma concentrations of lipid and apolipoprotein however, resulted in 1.7 times more rise in coronary atherosclerosis and three times more development in atherosclerotic aorta contrasted to steerage rabbits (Chen et al., 2019).

4.1.3 Oxygen deprivation-induced pulmonary high blood pressure in pigs for perceiving capnodynamic cardiac efficiency

Ten ventilated piglets within the average weight 23.9 kg are anaesthetized electrically and given mixture of hypoxic gas which triggers specific pulmonary hypertension. Pulmonary high blood pressure is eventually adjusted with breathed nitric oxide. Effective pulmonary blood flow (CO_{EPBF}), Fick method (CO_{Fick}) (Fick method is the cardiac output assessment) and pulmonary artery flow probe (CO_{TS}) are operated throughout the experiment (Karlsson et al., 2019).

4.2 Animal model of heart failure

Many small animal models have now been established over the past few centuries to depict multiple pathomechanisms that make a contribution to heart failure (HF). Notwithstanding some constraints, these animal models have significantly developed knowledge of the pathophysiology of the various HF aetiologies and made it possible for exploring the fundamental processes and effective treatment design. These models use clinical methods, genetic engineering and strategies of pharmacology (Riehle & Bauersachs, 2019).

4.2.1 Plinia cauliflora (Mart.) cardio safety for determining doxorubicin-influenced cardiac uncertainty rabbit model

Thirty female rabbits from New Zealand get six weeks of doxorubicin to produce heart failure. Plinia cauliflora extract (EEPC) is given by mouth for forty-two days at amounts of 75 and 150 milligram per kg regularly. Enalapril at the amount of 5 milligram per kg is given in the form of cardioprotective medicine. Blood compression and heart frequency are notified at the completion of the experiment (Romão et al., 2019).

4.2.2 In a pig model of heart failure with restored exaction percentage, Dapagliflozin enhanced left ventracular restoration work and aorta sympathy

Injecting a mixture of deoxycorticosterone acetate (DOCA) and angiotensin II (Ang II), also Western diet (WD) nourishing in pigs about eighteen weeks triggered heart failure by means of conserved expulsion fraction (HFcEF). Blood pressure, fat concentration, picture of heart through wide-ranging sound phase and cardiac blood movement aimed at cardiac dynamic and also practical modifications and also plasma and tissue levels of epinephrine and norepinephrine are evaluated. After nine weeks of therapy with dapagliflozin, in HFcEF pigs, blood compression, complete saturated fat, triglyceride and low-volume lipoprotein improved significantly, though only blood pressure decreased markedly (N. Zhang et al., 2019).

4.2.3 AST-120, Uremic toxin absorber, strengthen heart failure pathogenesis in rational dogs

In attempt to assess either blood concentrations of fluid overloaded poison indoxyl sulfate (IS) rise the minute of heart failure transpires or AST-120 may decrease these same concentrations and enhance HF, HF is generated by six weeks since fast right ventricle plodding at two hundred and thirty (230) beats/min in twelve beagle canines. After rapid ventricular pacing, six dogs are diagnosed with AST-120 for fourteen days. Six dogs of controlled group do not get any treatment (Asanuma et al., 2019).

4.3 Animal model of cardiac arrhythmia

There are various kinds of cardiac arrhythmias depending on their function and origin. The data collected from experimenting animals is vital in the expansion of testing besides therapeutic approaches; therefore, distinct animal models for separate kinds of arrhythmias are required (Bodhankar et al., 2005).

4.3.1 Human iPS-derived cardiac tissue of guinea pig cryo-injury study will not alter ventricular arrhythms

Human iPSC-evolved heart tissue (hEHT) is used in a model of guinea pig infarction to remuscularize wounded heart. Then, hiPSC-evolved hEHTs accelerated the occurrence of ventricular arrhythmias and ventricular arrhythmias are found in guinea pif after hEHTs insertion (Pecha et al., 2019).

4.3.2 Arctic modulates ischemia and cardiac tamponade by restricting oxidative stress in rats prompting ventricular irregular heartbeat

Rats are spontaneously subjected to sham operation (sham operation is a false surgical procedure that ignores the step considered therapeutically essential (Ciccozzi et al., 2016), single myocardial ischemia / cardiac tamponade, Arctigenin + myocardial ischemia/ cardiac tamponade, small (12.5 milligram per kg per day), intermediate (50 milligram per kg per day) as well as high (200 milligram per kg per day) with pretreated ATG, correspondingly. Ventricular arrhythmias have been evaluated. The incidence and length of ventricular conduction, ventricular profligate or speedy cardiac rate and ventricular ectopic or unbalanced heart beat are considerably reduced. Nevertheless, arrhythmia is suppressed (Al., 2018).

4.4 Other methods

4.4.1 Rat atrial epicardium electrophysiological monitoring with the help of a new stereotaxic instrument

A novel epicardial mapping scheme (CREAMS) for cardiac stereotactic electrophysiology

facilitates different readings, such as measurement of unipolar electrograms at various locations; placement of mapped locations and precise screening; assessment of electrophysiology at high-right atrium (HRA) location's in the *in vivo* Sprague-Dawley elevated-frequency stimulus rat study activated atrial fibrillation (AF). In a rat AF model, CREAMS has the ability for efficient electrophysiology evaluation through stereo placement and flexible working procedures (Fan et al., 2019).

4.4.2 Lessons through cardiac heartbeat and molecular docking of ion channel ligands with cardiotoxicity at Zebrafish

The zebrafish model can be used for high-throughput screening of drug libraries with prospective cardiotoxicity. Moreover, producing optional animal model of zebrafish, the basic ideologies of replacing, reduction and refinement (3R) for experimenting animal, could be accomplished (Sampurna et al., 2019).

4.4.3 Sapropterin treatment prevents hereditary pregestational diabetes metabolic abnormalities-generated hereditary cardiac abnormalities in mice

Streptozotocin triggered pregestational diabetes mellitus in full-aged female mice and nourished usual male mice for fertility. Prenatal mice are tested during gestation with sapropterin. Genomic assessment has defined CHDs. In the neonatal heart, cell proliferation, eNOS dimerisation and the production of reactive oxygen are evaluated (Engineer et al., 2018).

4.4.4 Heavy-fat nutrition-initiated cardiotoxicity heritage in institutional Drosophila

In Drosophila, pulmonary dysfunction caused by heavy-fat nutrition continues about two groups ahead to elucidate the processes of underlying risk of intergenerational heart disease (Guida et al., 2018).

4.4.5 A novel rabbit model for in-stent neoatherosclerosis

Neoatherosclerosis in-stent after percutaneous coronary intervention is a significant issue. An animal model is required to investigate the processes and treat in-stent neoatherosclerosis. Sixty rabbits have been split into three equivalent groups such as group A, the conventional method; group B, the standard operation method; and group C, the augmented methodFour weeks later, optical consistency tomography (OCT) screens all rabbits for neoatherosclerosis and no substantial distinctions in OCT information are discovered between new animal models and conventional and interventional groups. (G. Wang et al., 2019).

Chapter 5

Conclusion

The benefits of the review have paid the way to acquire knowledge about different animal models used in research areas and recent developments in cardiovascular disease treatment. By studying cells, tissues or body organs are not enough to gather knowledge about functions of the biological system of living organism. Animal models have given the chance to science to explore the functions, knowledge and information associated with the complex organ system of human body. In specific, when transferring from one platform to another, testing processes in appropriate models are necessary which produce extremely reproducible results, but, considering the spectrum of animal designs accessible today, a suitable approach is always feasible and animal designs are still better suited for the comprehension of the process of diagnosis of human disease. Traditional treatments such as non-pharmacological choice of healthy diet, exercise etc. for managing cardiac diseases now have become archaic. Recent advancements in all sectors such as surgery, heart imaging, drug market, non-invasive cardiac treatment and gene therapy etc. have replaced the traditional methods. As cardiac diseases are causing leading death worldwide, it has become a foremost duty to save the lives with new technologies and new developments.

Future Aspects

By this time it has been known that animals are crucial for exploration new advancements. In terms of cardiovascular disease animals have played vital role for investigating and quantifying new rehabilitations, new drugs as well as new personalized medicines etc. In the newer future animals will pave the way to explore new things and cardiac disease will be easily accomplished. Personalized medicine for cardiac patients, animal offspring as per research need, any genetically mutation that causing cardiovascular disease, pathologists for animal caring and handling and moreover, support for imaging human heart, maintaining a distinctive cultivars are the near future targets. In addition, it cannot be avoided that experiments in animal are the far most actual method for investigating both *in vitro* and *in vivo*. To compendium, animals scrutinized for the aim of cardiac disease supervision are not only meant for the study of present times but also for the analysis of future prospects.

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