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Insights and treatment strategies for coronary artery disease

Abstract

Coronary artery disease (CAD), which is also referred to as coronary heart disease (CHD) is a condition in which coronary arteries are unable to supply oxygen-rich blood to the heart muscle. There is no cure for CAD, but it can be managed through revascularization strategies that will be discussed in this review, such as the less invasive strategy of percutaneous coronary intervention (PCI) and the more invasive surgical option, coronary artery bypass grafting (CABG). In this review, we will cover the physiology of normal coronary circulation and the pathophysiology of atherosclerotic plaque formation. This review will also include an analysis of the coronary artery disease market, specifically the PCI market and the CABG market. Finally, this review will discuss emerging tissue engineering approaches to CAD treatment that incorporate more biologically integrated or regenerative strategies.

Keywords: coronary artery disease, percutaneous coronary intervention, coronary artery bypass grafting, revascularization, tissue engineering, regenerative medicin

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Abbreviations: CAD, coronary artery disease; CHD, coronary heart disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; IHD, ischemic heart disease; RCA, right coronary artery; LMCA, left main coronary artery; LAD, left anterior descending artery; LCx, left circumflex artery; SA, sinoatrial; AV, atrioventricular; SIHD, stable ischemic heart disease; ACS, acute coronary syndrome; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; ECG, electrocardiogram; LDL, low-density lipoprotein; BMS, bare-metal stent; DES, drug-eluting stent; BVS, bioresorbable vascular scaffold; ePTFE, expanded poly-tetrafluoroethylene; PET, polyethylene terephthalate; GDES, gene and drug-eluting stent; TGFβ, Transforming Growth Factor beta 1; PLGA, poly(lactic-co-glycolic acid); VEGF-A, vascular endothelial growth factor A

Introduction

CAD is characterized as the progressive narrowing or obstruction of the coronary arteries. This is caused by a buildup of fatty deposits known as plaque. The buildup of substances like fats and cholesterol on and within the artery walls leads to the narrowing of arteries, ultimately limiting oxygen-rich blood flow to the myocardium.[1] This condition is known as atherosclerosis, a condition which usually causes CAD.[2] Over time, this restriction of blood supply can lead to angina, myocardial infarction, heart failure, and sudden cardiac death.[3] CAD remains the primary cause of death in the world, as it is the leading single cause of death lost in the United States and worldwide.[2] The pathophysiology of CAD involves the accumulation and eventual rupture of plaque within the walls of coronary arteries, leading to platelet aggregation and thrombus formation that occlude the coronary artery.[4] There have been significant advancements in interventional revascularization strategies, especially with the development of stents used for coronary arteries, but the complications of these treatments highlight the need for further research that improves the outcomes of patients with CAD.

Market size and trends

Market size

CAD is the third leading cause of mortality worldwide and the leading cause of mortality in the United States, accounting for approximately 17.8 million deaths worldwide and 610,000 deaths in the United States annually.[5] As of 2018, 16.5 million people over the age of 20 were diagnosed with CAD.[6] Ischemic heart disease (IHD), of which CAD is the primary cause, has more of a global burden than any other illness in the developed world, as it causes more deaths and incurs more of an economic cost than any other illness, with 15.5 million people in the United States alone being diagnosed with IHD.[7]

Despite the substantial prevalence of CAD, the prevalence and mortality rates of CAD have been decreasing in developed countries, which can be attributed to increased awareness of disease prevention, risk factor identification, and advances in medical technology in the past several decades.[5,6] The mortality rate of CAD has experienced a downward trend for decades, as mortality data gathered starting from 1969 has concluded that by 2020, the number of heart disease-related deaths would decrease by 21.3% for men and 13.4% for women (Figure 1).[5] The decline in morbidity and mortality of CAD is largely attributed to the early identification of risk factors and the implementation of effective primary prevention strategies.[8] Increased awareness of lifestyle modifications including diet, exercise, and cessation of smoking reducing the risk of CAD, and the widespread use of risk assessment and preventative therapies are responsible for the decline in CAD mortality in developed countries.[9] However, the burden of CAD (measured by disability adjusted life years) is projected to increase globally.[10]

The age distribution of CAD is majorly skewed towards older populations, with age being the strongest factor in the development and mortality of CAD when coronary atherosclerosis manifests (Figure 2).[12] The prevalence of risk factors such as diabetes and

hypertension is prevalent in young patients with CAD, but the prevalence of these risk factors is much higher in older patients with CAD.[13] Older patients are a high-risk population for CAD, both in the development of CAD and mortality from CAD (14). Due to the increase in life expectancy over time, the burden of CAD will also see increases over time.[15]

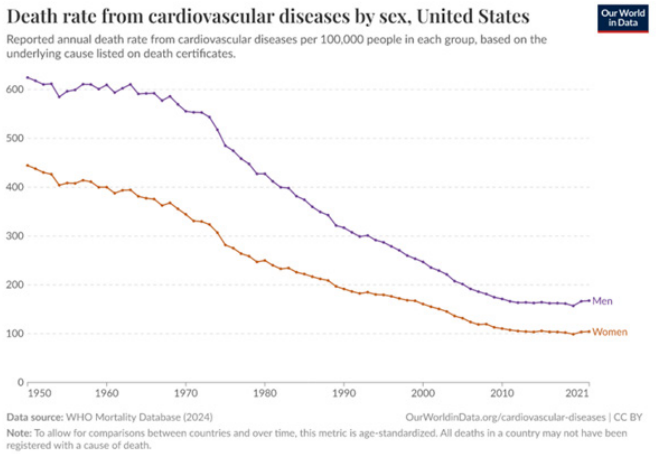

Figure 1 Death rate from cardiovascular diseases by sex in the United States.[11]

This image shows the death rate from cardiovascular diseases between men and women in the United States from 1950 to 2021.

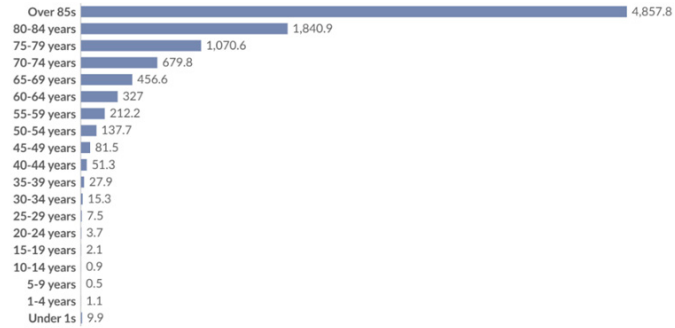

Figure 2 Death rate from cardiovascular diseases by age group, United States, 2021.[11]

This image shows the total death rate of cardiovascular diseases in the United States in 2021, separated by age groups.

In terms of economic impact, CAD places a substantial financial burden on healthcare systems, illustrated with the healthcare services for CAD having an estimated annually cost exceeding 200 billion dollars in the United States.[16] In the United States, the cost of managing cardiovascular diseases, of which CAD is a major contributor, is projected to almost triple from $627 billion in 2020 to $1851 billion in 2050. The total economic burden for CAD specifically is projected to increase by 124% from $260 billion in 2020 to $584 billion in 2050 (Figure 3).[17]

Currently, treatment for CAD relies on either PCI or CABG as methods for revascularization.[18] Around 650,000 revascularization procedures for CAD are performed in the United States annually, with around 450,000 PCIs and 200,000 CABG operations.[19] However, advances in medical therapy and the increased adoption of appropriate-use criteria have led to a reduction in the number of revascularization procedures performed.[19] CABG has an operative mortality rate of below 2.7% and has a slight survival benefit over PCI but only by less than 0.2%.[20]

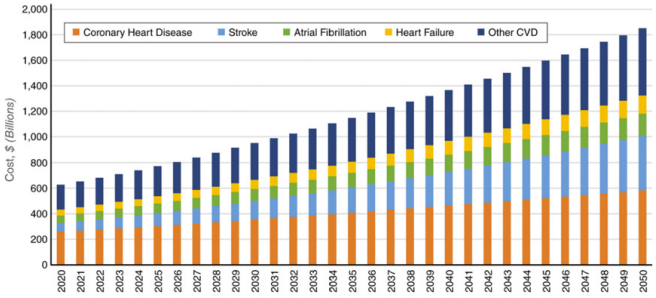

Figure 3 Population-level economic burden of cardiovascular disease and stroke in US adults, by condition, 2020 to 2050.[17]

This image shows the cost of coronary heart disease, stroke, atrial fibrillation, heart failure, and other cardiovascular diseases for adults in the United States, projecting from 2020 to 2050.

Approximately 5% of adults aged 20 and older are affected by CAD, and the number of people suffering from CAD is still rising due to an aging population and contributing factors such as sedentary lifestyles and unhealthy diets.[21] The increase in people with CAD has led to a greater demand for coronary stents (included in PCI) as a treatment for patients with blocked narrowed arteries, causing a continuous increase in the global coronary stents market (Figure 4).[21] As shown in Fig. 6, the global coronary stent market was valued at $8.3 billion and is projected to grow by 2.6% from 2025 to 2030.[21] The global CABG market is also growing (Figure 5), and this growth can largely be attributed to increases in people developing myocardial infarctions, as well as increases in the geriatric population which are at highest risk for CAD.[22] As shown in Figure 5, the global CABG market was valued at $12.98 billion in 2023 and is expected to grow by 9.4% from 2024 to 2030.[22]

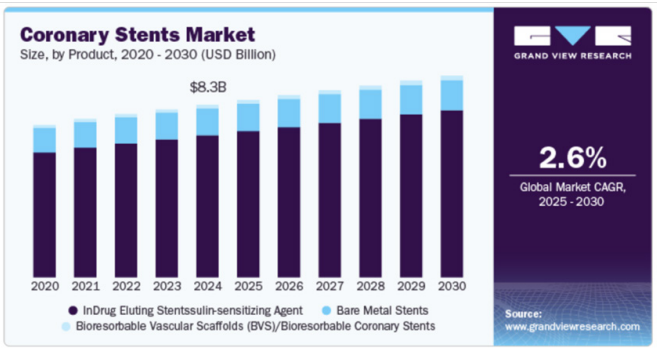

Figure 4 Global coronary stents market.[22]

This image shows the size of the global coronary stents market from 2020 projected to 2030, including the size of the drug-eluting stent, bare-metal stent, and bioresorbable vascular scaffolds/bioresorbable coronary stent markets.

Market Segment and trends

The CAD market can be divided based on the procedures used to treat CAD, which are PCI (performed using coronary stents) and CABG.[24] PCI and CABG are the primary procedures utilized for revascularization when arteries are narrowed or completely obstructed.[25] Therefore, the CAD market is divided into the coronary stent market and the coronary artery bypass graft market. The coronary stent market is increasing due to an increase in the demand for coronary stents, and this increase in demand is caused by the advancements in bioavailability for coronary stents.[23] The market is classified into three products: drug-eluting stent, bioresorbable

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vascular scaffold (BVS), and bare metal stent (Figure 6).[23] The drug-eluting stent generates the highest revenue out of the three products with a generated revenue of $6.4 billion USD in 2024, Figure 6 and a major benefit of the drug-eluting stent compared to bare-metal stents is the ability to deliver drugs to prevent excess tissue growth, lowering the risk of restenosis.[26] Bioabsorbable stents also offer an alternative with promising outcomes, ideally minimizing the invasiveness for high-risk patients due to the ability of BVS to build a scaffold that temporarily supports the stent before dissolving in the body after the artery is healed, which eliminates risk of morbid thrombosis.[27] As seen in Figure 8, the benefits that drug-eluting stents and BVS provide cause these products to take up a larger portion of the coronary stent market.

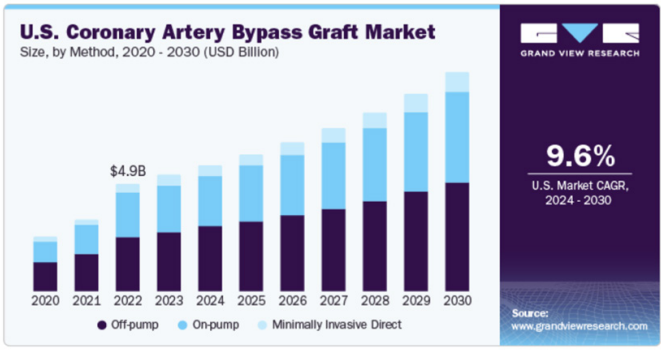

Figure 5 Global coronary artery bypass graft market.[23]

This image shows the size of the global coronary artery bypass graft market from 2020 projected to 2030, including off-pump, on-pump, and minimally invasive direct graft markets.

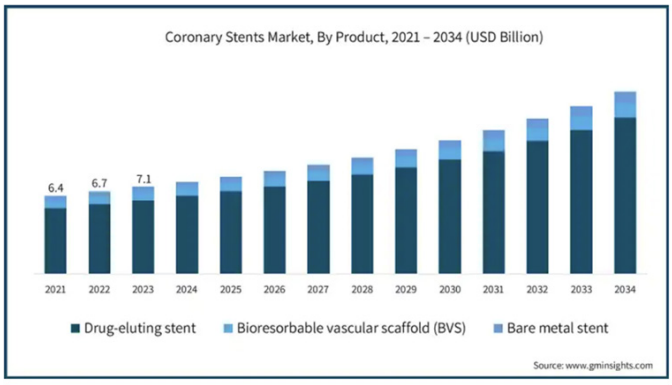

Figure 6 Coronary stents market analysis by product.[23]

This image shows the size of the global coronary stent market by product, including the sizes of the drug-eluting stent, bioresorbable vascular scaffold, and bare metal stent markets.

CABG uses a graft to restore blood flow to the heart, often involving taking a section of a blood vessel from the leg or chest.[28] The growth in the CABG market can be attributed to the growing prevalence of CAD globally and the growing elderly population, who are at highest risk for CAD.[29] The CABG market is classified into grafts, retractors, heart positioners, tissue stabilizers, and other products, with grafts generating the highest revenue with $3.1 billion USD in 2023 (Figure 7).[29] Advancements in the manufacturing methods of grafts, especially with the introduction of drug-eluting grafts and tissue engineering to manufacture highly compatible blood vessels, increase the effectiveness of CABG and increase the demand for grafts.[30]

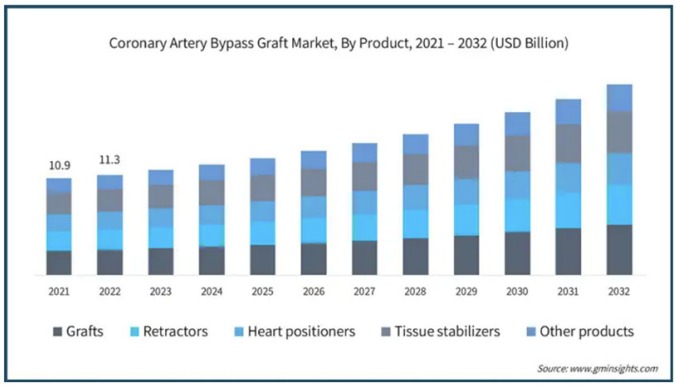

Figure 7 Coronary artery bypass graft market analysis by product.[29]

This image shows the size of the global coronary artery bypass graft market by product, including the sizes of the market for grafts, retractors, heart positioners, tissue stabilizers, and other products.

Physiology of the heart

Normal physiology of coronary circulation

Coronary circulation is an essential process for the homeostasis of the body, as it is responsible for supplying oxygenated blood to the heart.[31] The coronary arteries are located on the surface of the heart, originating from the root of the aorta.[31] The coronary arteries consist of two primary arteries: the right coronary artery (RCA) and the left main coronary artery (LMCA), which both originate from the root of the ascending aorta (Figure 8).[32]

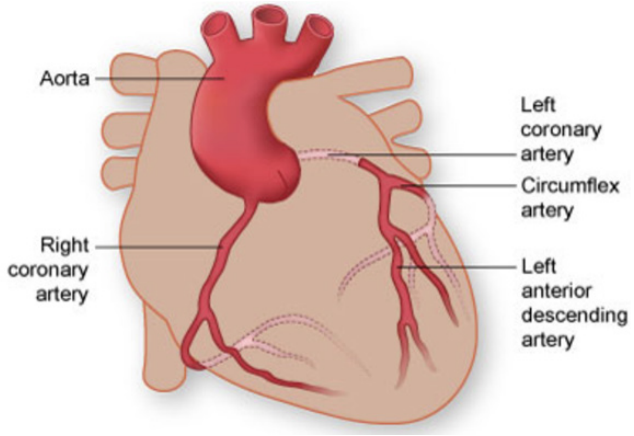

Figure 8 Anatomical depiction of the coronary arteries and coronary circulation.[34]

This image shows the anatomical position of arteries in relation to the overall heart structure, including the location of the aorta, right coronary artery, left coronary artery, circumflex artery, and left anterior descending artery.

The RCA stems from the anterior ascending aorta and primarily supplies blood to the right side of the heart, consisting of the right atrium and right ventricle.[34] One key branch of the RCA is the sinoatrial nodal artery, which supplies the SA node, and the RCA also supplies the AV node in 90% of people.[33] The RCA then splits into smaller branches including the posterior descending artery, which is responsible for blood supply to the anterior two-thirds of the septum, and the acute marginal artery.[33]

The LMCA is divided into two major branches: the left anterior descending artery (LAD) and the left circumflex (LCx) coronary

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artery (Figure 8).[31] The LAD supplies blood to the anterior portion of the left ventricle whereas the LCx artery supplies blood to the left atrium and the posterolateral portion of the left ventricle, so these two branches combined are responsible for blood supply to the left.

Disease

CAD is caused by atherosclerotic plaque formation, and the likelihood of this is increased by modifiable risk factors including smoking, obesity, lipid levels, and hypertension.[35] CAD can either manifest as stable ischemic heart disease (SIHD) or acute coronary syndrome (ACS).[36] SIHD presents as stable angina, and it involves fixed atherosclerotic plaques that narrow the coronary arteries and limit blood flow during exertion but allow for adequate perfusion at rest.[37] Although SIHD may manifest with atypical symptoms, it primarily manifests with substernal chest pain or pressure that worsens with exertion and is relieved with rest and nitroglycerin treatment.[38] SIHD patients often develop chronic worsening of angina symptoms, eventually leading to the development of ACS, which refers to acute events caused by plaque rupture, thrombosis, and sudden obstruction of a coronary artery.[37,39] ACS is a group of conditions that includes ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina.[40] Unstable angina is characterized by chest pain that occurs at rest and is often a precursor to myocardial infarctions.[41] STEMI and NSTEMI unstable angina are differentiated through the use of an ECG (22). STEMI occurs through the complete and persistent occlusion of a coronary artery, whereas NSTEMI is caused by severe coronary artery narrowing.[42]

The etiological factors of CAD can be categorized as either nonmodifiable or modifiable.[43] The nonmodifiable factors include gender, age, genetics, and family history, especially with men being more predisposed to CAD than women.[44] The traditional modifiable factors include hypertension, smoking, obesity, diabetes mellitus, and lipid levels.[45] Elevated high-density lipoproteins increase CAD incidence, which is seen in how inherited lipid disorders such as hypercholesterolemia can significantly accelerate atherosclerosis and increase the risk of CAD.[45] Smoking remains the leading cause of cardiovascular disease, and obesity is linked to increased cardiovascular risk and greater risk of developing CAD.[44]

CAD typically presents as angina pectoris, which presents as a gradual onset of pain in the chest, particularly behind the sternum.[44] The pain often radiates to the left arm, shoulder, arm, neck, or jaw.[46] Angina pectoris can be classified as either stable or unstable angina, where stable angina is triggered by physical exertion while unstable angina can occur suddenly and even at rest.[44] In more severe cases, this can manifest as progression into myocardial infarction or sudden cardiac death. CAD can also cause atypical presentations that are less prevalent than angina pectoris, with the atypical pain occurring in the epigastric region or back, and is presented as burning, stabbing, or indigestion sensations.[47] In addition to angina pectoris, CAD can also cause shortness of breath, nausea, and dizziness.[44]

Pathophysiology

The core process driving CAD is atherosclerotic plaque formation (Figure 9), since atherosclerosis is the primary cause of CAD.[44] Plaque formation occurs through a buildup of fatty material, which impedes blood flow due to narrowing of the arterial lumen.[48] The first step in plaque formation is the formation of a "fatty streak", which is initiated when the endothelium is damaged.[49] In response to this damage, monocytes migrate into the subendothelial space and differentiate into macrophages.[50] These macrophages take up oxidized LDL particles, leading to the formation of foam cells, which will aggregate to form plaque. The inflammation occurring from the damage is worsened due to T cell activation and the release of cytokines. Smooth muscle cells also internalize oxidized LDL particles and collagen, contributing to the formation of foam cells and helping to form the fibrous caps that stabilize plaque, ultimately promoting plaque growth and stability.[50] From this process, a subendothelial plaque develops over time.[44]

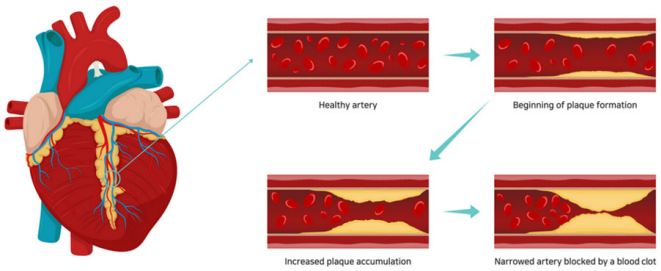

Figure 9 Diagram depicting the stages and progression of atherosclerosis.[51]

This image depicts the process of atherosclerosis, from healthy artery to beginning of plaque formation, and progressing to increasing plaque accumulation and to narrowed artery blocked by a blood clot.

After plaque forms, it can either continue growing or stabilize if no further damage occurs.[44] If the plaque is stable and macrocalcification (large calcium deposits) of the lesion occurs, a fibrous cap made of a collagen-rich extracellular matrix provides structural stability, resulting in a stable lesion. Macrocalcifications are the accumulation of smaller calcium deposits, evolving into calcified sheets and plates, stiffening the artery wall over time. If the lumen has at least 70% obstruction due to lesions, this causes insufficient myocardial tissue perfusion which triggers angina (chest pain) symptoms during times of increased oxygen demand.[44] However, some plaques remain unstable, characterized by a thin fibrous cap and microcalcifications (small calcified deposits) that increase mechanical stress within the fibrous cap, making the plaque more prone to rupture.[52] Microcalcifications are formed when smooth muscle cells release calcifying extracellular vesicles and undergo apoptosis, which form small calcified deposits.[52] If the plaque ruptures, this exposes tissue factor to the bloodstream, which triggers thrombosis (clot formation) that causes the partial or complete obstruction of the lumen (Figure 10).[53]

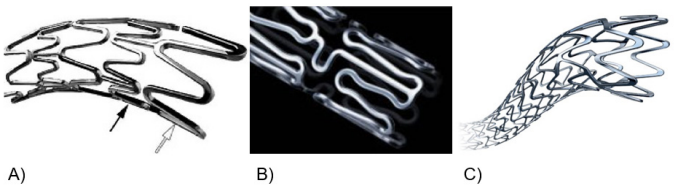

Figure 10 Images of commercially available bare-metal stents. A) Express by Boston Scientific (stainless steel) (55). B) MULTI-LINK VISION Coronary Stent System by Abbott Cardiovascular (cobalt chromium alloy (56). C) Omega BMS by Boston Scientific (platinum chromium alloy).[57]

This image depicts three types of bare-metal stent products in the market made from different types of metal, which are Express (by Boston Scientific), MULTI-LINK VISION Coronary Stent System (by Abbott Cardiovascular), and Omega BMS (by Boston Scientific).

Existing products

Percutaneous coronary intervention

PCI has been established as the optimal treatment strategy for STEMI patients, with coronary stenting causing immensely better

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reperfusion and lower risk than alternatives.[54] The earliest attempt for PCI that reached the safety and efficacy for PCI procedures to enter mainstream clinical practice was the introduction of the bare-metal stent. Bare-metal stents are characterized as small expandable wire mesh tubes that are implanted into blood vessels. Earlier bare-metal stents were constructed with stainless steel, and were able to effectively maintain blood vessel patency.[54] Implantations of balloon-expanding stents revealed better performance, but there were still major limitations with the prevalence of neointimal growth and late restenosis.[55] A reduced strut thickness lessens the localized inflammatory responses that drive in-stent restenosis, so there was a shift in stent architecture from the use of 316 L stainless steel to cobalt chromium, which reduced the strut thickness without loss of radial strength. Although drug-eluting stents are currently considered the default option for PCI, bare-metal stents still take up a sizeable portion of stent procedures due to the reduced cost and the more rapid reendothelialization improving the safety for high bleeding risk patients.[54]

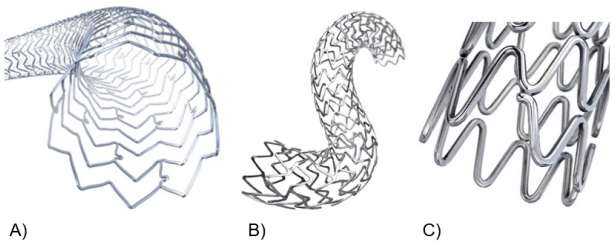

Figure 11 Images of commercially available drug-eluting stents utilizing drugs in the limus family. A) Xience by Abbott Cardiovascular (everolimus).[60] B) Promus ELITE by Boston Scientific (everolimus).[61] C) Resolute Onyx by Medtronic (zotarolimus).[57]

This image depts three types of drug-eluting stent products in the market that use different drugs, which are Xience (by Abbott Cardiovascular), Promus ELITE (by Boston Scientific), and Resolute Onyx (by Medtronic).

Drug-eluting stents were initially developed by coating bare-metal stents with an anti-proliferative agent which localized arrest of the smooth muscle cell proliferation cycle around the implanted stent and therefore limited in-stent restenosis. However, first-generation drug-eluting stents caused a delayed and incomplete reendothelialization around the stent struts due to the anti-proliferative agent, which led to increased rates of stent thrombosis.[58] Second-generation drug-eluting stents massively improved upon first-generation drug-eluting stents, making significant changes to major components of a drug-eluting stent.[58] The backbone of the stent was changed from a thicker stainless steel material to chromium-based alloys (cobalt chromium or platinum chromium), which reduced the thickness of the stent and therefore improves endothelialization. Novel drugs were also introduced, specifically drugs in the limus family such as everolimus and zotarolimus, and more recently extensions to urimolimus, novolimus, and amphilimus due to these drugs reducing vascular inflammation and promoting better endothelialization as well as being shown to transmit better through hydrophobic arterial tissue. Notable examples are everolimus used in Xience by Abbott Cardiovascular and Promus by Boston Scientific, and zotarolimus used by Endeavor and Resolute stents by Medtronic (Figure 11).[55] Polymer coatings were also enhanced to reduce the late-stent thrombosis occurring from hypersensitivity, with the use of abluminal coatings to minimize polymer exposure in order to minimally affect endothelialization and therefore decrease thrombosis.[59] These changes implemented in second-generation stents helped alleviate the late-stent thrombosis present in first-generation drug-eluting stents (Table 1).

Table 1 Second generation drug-eluting stent products[55]

Stent	Drug	Drug material	Manufacturer
Resolute Integrity	Zotarolimus	Cobalt chromium	Medtronic
Endeavor Resolute	Zotarolimus	Cobalt chromium	Medtronic
Resolute Onyx	Zotarolimus	Cobalt chromium with platinum chromium core	Medtronic
Biomatrix	Biolimus A9	Stainless steel	Biosensors International
BioFreedom	Biolimus A9	Stainless steel	Biosensors International
Ultimaster	Sirolimus	Cobalt chromium	Terumo
Orsiro	Sirolimus	Cobalt chromium	Biotronik
Xience Prime	Everolimus	Cobalt chromium	Abbott Cardiovascular
Promus Premier	Everolimus	Platinum chromium	Boston Scientific
Synergy	Everolimus	Platinum chromium	Boston Scientific

Bioresorbable stents have been a newer development, with the goal of supporting the artery with the scaffold, elute antiproliferative drugs, and allow the device to resorb the scaffold months after deployment. The approach aimed to restore the natural vasoactivity of arteries and improve blood flow over time. Full resorption of the device also eliminates stiffening of the artery at the implantation site and therefore restores physiological shear stress, and also aimed to reduce the restenosis and late-stage thrombosis caused by inflammatory responses. However, adverse clinical outcomes emerged over time, with complications such as faster-than-expected degradation and early loss of scaffolding causing restenosis rates higher than that seen in drug-eluting stents. Additionally, the process of strut resorption potentially amplifies late-stent thrombosis. Despite this, there are some notable bioresorbable vascular scaffolds, with a significant product being ABSORB III by Abbott Cardiovascular which is in clinical trial, developed from ABSORB I and ABSORB II.[55]

Drug-eluting balloons have also been introduced as an alternative to second generation drug-eluting stents, where temporary scaffolding and drug transfer occurs in place of long-term or permanent implants. The goal of drug-eluting balloons was to avoid chronic inflammatory responses in the vasculature caused by implants, and to improve the healing process.[62] Drug-eluting balloons are especially targeted for clinical applications where permanent devices would be less successful, including peripheral arterial diseases and atherosclerosis in bifurcations. Drug-eluting balloons have shown varying degrees of efficacy depending on the design and therapeutic agent, improving on the magnitude of in-stent restenosis but showing mixed results in the efficacy of treating de novo CAD.[55]

Coronary artery bypass grafting

CABG is a major surgical operation used to treat severe CAD by improving blood flow to the heart muscle. Blocked coronary arteries are bypassed using veins or arteries taken from other parts of the body, which restores blood flow to the ischemic myocardium which helps to restore heart function and tissue viability, as well as relieving angina symptoms. CABG is the most commonly performed major surgery procedure, with almost 400,000 procedures performed annually.[63] CABG procedures can be categorized as either on-pump or off-pump

CABGs, with the difference being the use of a cardiopulmonary bypass circuit and an arrested heart to operate during an on-pump CABG whereas the heart remains beating for an off-pump CABG.[64] CABG is performed over PCI when there are high-grade blockages in any major coronary artery, or when PCI has failed to clear blockages from the arteries. Commonly, blood vessels are taken from the saphenous vein from the leg or the internal thoracic artery, so saphenous vein grafts and internal thoracic artery grafts are some of the most notable CABGs. The graft is attached to the aorta or another large artery, and is sewn beyond the blockage in the coronary artery, allowing for a new path to form for oxygen-rich blood to reach the myocardium. The products involved with CABG are the medical devices and instruments required to harvest the graft and perform the attachment, including graft harvesting tools and surgical instruments.[63]

Some categories of products used include retractors, heart positioners, and tissue stabilizers, which are all used to facilitate surgical procedures. A major category for products used is synthetic or biological grafts, which are used when autologous vessels are not available or are limited.[65] The main synthetic graft materials used in vascular reconstructions are expanded poly-tetrafluoroethylene (ePTFE) and woven polyethylene terephthalate (PET), which is also known as Dacron. Some biologic vascular grafts and tissue engineered grafts have been applied, but most of them have experienced failure due to thrombogenicity.[66]

Products in development

Products in pre-clinical trials

Although there has been significant progress throughout the years in improving drug-eluting stents, the optimum drug-eluting stent has yet to be established due to the complications that still occur with implantation. In-stent thrombosis is still a major issue with drug-eluting stents, and potentially lethal consequences of drug-eluting stents need to be eliminated.[67] There have been methods emerging that attempt to implement upgrades to stent components and delivery systems, addressing inadequacies of the stents currently available. Gene-eluting stents have been identified as one of the most promising methods of upgrading the effectiveness of drug-eluting stents, especially for decreasing risk of excess inflammation and restenosis due to localized genetic exchange to the vascular system.[67]

A baculoviral gene and drug-eluting stent (GDES) has been developing in order to promote the reendothelialization and prevent the restenosis caused by atherosclerosis. The TGFβ1 gene regulates smooth muscle cell proliferation and extracellular matrix secretion, promoting endothelial cell proliferation and inhibiting smooth muscle cell hyperproliferation. A pre-clinical trial of a GDES releasing both the therapeutic TGFβ1 gene and the drug Everolimus was designed in order to improve artery healing, prevent artery narrowing, and reduce the inflammation that occurs after implantation of a drug-eluting stent. PLGA nanoparticles were loaded with TGFβ1 expressing baculoviruses and were prepared by a double emulsion solvent evaporation method. A bare-metal stent was dipped into a solution containing Everolimus, and genipin-carrying baculoviruses expressing TGFβ1 in nanoparticles. The GDES slowly releases both the gene and the drug over a controlled period, using in vitro and in vivo methods to assess the functionality and safety of the GDES. The GDES was shown to facilitate efficient healing of the inner artery line and reduced inflammation as well as abnormal smooth muscle cell growth. The TGFβ1 gene also promoted healthy endothelial cells, while Everolimus helped prevent excessive tissue growth. Additionally, the stent itself was demonstrated to be non-toxic and safe for contact with blood, and the stent coating was stable during and after gradual degradation occurred. Therefore, the GDES using the TGFβ1 gene and Everolimus has shown promise in promoting healing and reducing the risk of in-stent restenosis, indicating the great potential in combining gene therapy and drug delivery in stents for treatment of CAD.[68]

A GDES using adenoviral gene transfers of vascular endothelial growth factor-A (VEGF-A) and LacZ (used as a control marker) were performed with a ClearWay RX infusion balloon catheter on both stents. A study was conducted with these two genes, testing the efficacy of VEGF-A and LacZ delivered directly into the artery using an infusion balloon catheter for its ability to promote vessel recovery after stenting, since vessel recovery after stenting has been a critical factor in reducing possible complications after stent implantation. VEGF-A was administered as a method to stimulate rapid reendothelialization after stent implantation to prevent restenosis. For this experiment, the luminal gene therapy was administered in a pig coronary artery restenosis model. In arteries with bare-metal stents and VEGF-A, reendothelialization after stenting occurred faster than the other methods tested using bare-metal stents. The bare-metal stent treated with LacZ experienced the highest restenosis. When VEGF-A was used with a drug-eluting stent, there was no significant improvement in restenosis rates compared to just the drug-eluting stent alone. Delivering gene therapy via the ClearWay RX infusion balloon catheter with VEGF-A was proven to be safe and tangible. The administration of VEGF-A improved the reendothelialization when utilizing a bare-metal stent, but did not induce much change in the reendothelialization when utilizing a drug-eluting stent. Therefore, this gene therapy does not add benefits to drug-eluting stents in the short-term, so future work is needed for the combination of the VEGF-A gene and drug-eluting stents to develop into a product used to treat CAD.[69]

Products in clinical trials

The default technique for PCI is implantation of a drug-eluting stent, but the approach of deploying a balloon coated with an antiproliferative drug (a drug-coated balloon) has been presented as a viable alternative. Drug-coated balloons are transferred to the luminal surface of a lesion for implantation. This method presents zero risk of thrombosis, as the antiproliferative drug is directly delivered to the vessel wall without leaving a permanent stent.[69] It also dilates and treats the lesion while promoting more physiological remodeling and preserving natural vessel flexibility, but holds risks in recoiling and risk of dissection that led to stents being implemented in the first place. Drug-coated balloons have been available for use, but mostly for in-stent restenosis and small vessel disease thus far, and it is yet to be determined if drug-coated balloons will find a role in complex PCI.[70]

The efficacy and long term impact of drug-coated balloons compared to drug-eluting stents for treating patients with de novo coronary artery lesions was assessed through a clinical trial (REC-CAGEFREE I). The clinical trial aimed to evaluate whether a paclitaxel-coated balloon is as safe and effective as a traditional drug-eluting stent, specifically a sirolimus-eluting stent in patients undergoing PCI for de novo lesions. Patients in China with de novo coronary lesions were treated with either the paclitaxel-coated balloon or a sirolimus-eluting stent (Firebird 2), and the outcomes were assessed up to 24 months after implantation. The outcomes for small vessels, where the device diameter was under 3.0 mm, were similar between the drug-coated balloon and the drug-eluting stent, evaluated by observing the revascularization, thrombosis, and mortality rates. However, the outcomes for larger vessels were significantly worse in the drug-coated balloon than the drug-eluting stent. The safety of the

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drug-coated balloon and the drug-eluting stent were comparable as the rates of bleeding and in-stent thrombosis were similar for the two devices, but the drug-coated balloon was associated with higher rates of revascularization and a trend towards higher mortality rates. These findings suggest that drug-eluting stents still remain the preferred treatment strategy for de novo coronary lesions, especially in larger vessels, The potential for drug-coated balloons is interesting, but needs more clinical testing to become a primary method of treatment for CAD.[70]

Although there needs to be more development in drug-coated balloons for treatment of de novo coronary artery lesions, there is also potential for the device to be utilized in treating coronary bifurcation lesions during PCI. In bifurcations, an artery splits into two branches (a main and a side branch), and placing a stent in the side branch can be especially difficult. Early studies have shown that using drug-coated balloons for the side branch has potential as a method, demonstrating safety and feasibility. In the ongoing clinical study, patients with new bifurcation blockages will either receive a hybrid approach of using a drug-coated balloon in the side branch or will receive a two-stent approach of placing a drug-eluting stent in the side branch. The outcomes of the two strategies are compared by tracking the all-cause death, heart attacks, and repeat procedures on the treated artery over a two-year follow up. This study will help determine if using a drug-coated balloon on the side branch of a coronary bifurcation lesion is a viable alternative to the more complicated two-stent technique for patients with bifurcation lesions.[71]

For patients with PCI receiving a stent to treat severely calcified lesions, the severe coronary artery lesion calcification can make the procedure they receive much more difficult, increasing the risk of complications and causing poor stent expansion which leads to adverse effects that are not fully established. Orbital atherectomy is a technique used to shave away calcium from artery walls before stent placement, and it is hypothesized that this may improve outcomes by helping the stent expand more fully. A clinical study aimed to compare orbital atherectomy and balloon angioplasty, with both methods followed by drug-eluting stent implantation. The goal was to examine if orbital atherectomy reduced the rate of target vessel failure at one year, heart attack in the treated vessel, or repeat procedures to fix the same artery. Orbital atherectomy could also improve stent expansion. The results of the clinical trial indicated that using orbital atherectomy before stenting was comparable to a balloon angioplasty-first strategy in reducing major cardiac events and improving stent expansion for patients with severe coronary calcification. These results suggest that future research is required in order for orbital atherectomy to be a viable alternative to balloon angioplasty when treating severely calcified lesions for patients with PCI (Appendix).[72]

Conclusion and future considerations

CAD remains one of the leading causes of morbidity and mortality worldwide. The treatment landscape of CAD has significantly advanced over recent decades, especially within the strategies of PCI and CABG, leading to an improvement in patient outcome overall. Improved outcomes have been driven by aggressive risk factor modification, advancements in medical therapy, and the progression of revascularization strategies especially regarding PCI and CABG. Despite the advancements in revascularization that have added immense clinical benefits to the treatment of CAD, there are still significant complications to revascularization strategies that have not been fully addressed, stemming from the complications associated with devices used for PCI. Drug-eluting stents have significantly reduced rates of in-stent restenosis compared to bare-metal stents, but there are still heavy concerns regarding late-stent thrombosis, delayed reendothelialization, and long-term impacts on vascular physiology that are illustrated with the complications occurring with the implantation of drug-eluting stents.

In order to address the constraints of cardiovascular stents, namely in-stent thrombosis, in-stent restenosis, and delayed reendothelialization, new methods have been identified in attempting to optimize coronary stents to address the sub-optimal long-term outcomes of stent implantation. Recent clinical studies highlight that while significant innovations such as drug-coated balloons have shown potential, these products have not been able to demonstrate superiority over conventional stenting in broader patient populations. The optimal cardiovascular stent system has yet to be established, but there are several methods including gene-eluting stents that attempt to improve on the currently established coronary stents. Therefore, to mitigate stent-related complications, further research is warranted to enhance long-term safety and clinical outcomes by providing next-generation drug-delivery platforms and bioresorbable scaffolds. The future of CAD treatment also will likely focus on greater use of image-guided PCI and integrating artificial intelligence to predict adverse outcomes. Ultimately, although many advancements have been made over time for the treatment of CAD, further research is needed to address the complications that current CAD treatment methods cause.

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Conflict of interest

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