A Review Of Biomedical Devices Used For The Treatment Of Intravascular Calcification With A Proposed Screening And Treatment Algorithm To Significantly Reduce The Incidence Of Heart Attacks And Deaths Due To Cardiovascular Disease

IE 5356: Biomedical Devices - Design and Manufacturing
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1 Abstract

Intravascular calcification is a primary cause of heart disease and heart attacks. In the United States, 659,000 people die each year from heart disease [1]. This translates to one death every 36 seconds and accounts for 25% of deaths in the US. From 2016-2017, the cost of health care pertaining to heart disease is $363 billion per year. This paper reviewed the various biomedical devices which have evolved over the past six decades and how their unique design and functional features made them suitable for the treatment of intravascular calcification. These devices include angioplasty balloons, stents, atherectomy devices, and the latest state-of-the-art shockwave intravascular lithotripsy (IVL) device. A treatment algorithm is proposed using a combination of different devices by taking advantage of their individual features. A public health perspective is also included in the discussion by combining a screening algorithm with the treatment algorithm to suggest and motivate the use of a strategy which may dramatically reduce the incidence of heart attacks, perhaps even eventually eliminate the need for bypass surgeries, and lower the number of deaths associated with cardiovascular disease.

2 Introduction: Coronary Calcification Risk Factors, Process and Evaluation

Coronary calcification increases with age. Risk factors include higher body mass index or obesity, high blood pressure, metabolic syndrome, dyslipidemia or abnormal lipids (high LDL and low HDL), lack of exercise, smoking or tobacco use, diabetes mellitus, and chronic kidney disease [2, 5]. Progression of calcification is illustrated in Figure 1 [3].

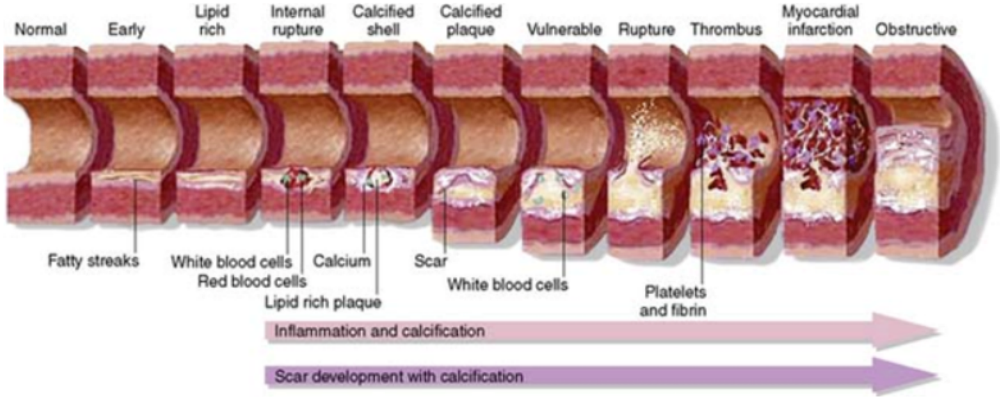


Figure 1: Artery Calcification [3].

Optical Coherence Tomography (OCT) is a non-invasive gold-standard imaging modality for assessing the calcification characteristics of each segment of a coronary artery. Together with the Ultreon 1.0 Software by Abbott [4], accurate measurements, including the Calcium Score, can be obtained. The Calcium Score is associated with the coronary plaque burden as follows [5]:

Calcium Score	**Coronary Plaque Burden**
0	No identifiable disease
1 to 99	Mild disease
100 to 399	Moderate disease
Greater than 400	Severe disease

Table 1: Association between calcium score and coronary plaque burden [5].

OCT and intravascular ultrasound (IVUS) are both used to guide interventional coronary procedures (that is, angioplasty, stenting, atherectomy, or shockwave IVL). IVUS mainly shows calcification within the lumemn or around the surface of the vessel wall but not in the deeper layers of the vessel.

3 Evolution of Biomedical Devices For Decalcification

In 1960, the first bypass surgery on a human was successfully performed by Goetz. Minimally invasive techniques and devices such as angioplasty balloons and stents were developed, followed by laser atherectomy, directional atherectomy and rotational atherectomy, However, bypass surgery remained the gold standard of treatment, especially for severe blockages of coronary arteries by calcific plaque until the number of these surgeries peaked at 519,000/year in the year 2000 in the United States. It took awhile for more doctors to be trained for greater adoption of the minimally invasive techniques, particularly as preventive measures. Subsequently, the number of bypass surgeries fell significantly to 300,000 in 2012 as atherectomies became the treatment of choice, Up to 2014, the use of bypass surgery had a 40% failure rate. Treatment using only angioplasty together with stents were not much successful either with a failure rate of 34%. Interestingly, the drop in number of annual bypass surgeries of about (519,000 - 300,000) = 219,000 seems to correspond with the 190,000 number of atherectomies carried out per year. After the development of orbital atherectormy and shockwave intravascular lithotripsy during the last decade, the failure rate of treatment in fully-equipped hospitals had dropped to less than 5%. [6]

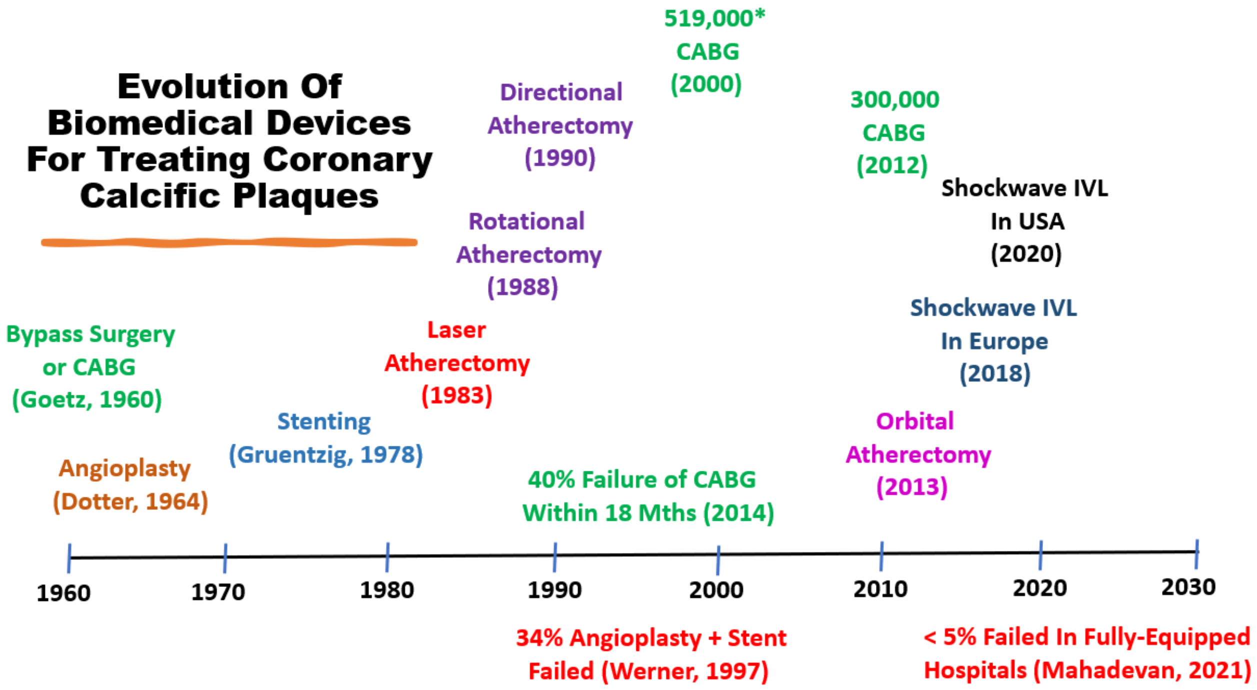


Figure 2: Evolution of biomedical devices for treating calcific plaques.

4 Design, Functional Aspects, And Limitations Of Techniques And Biomedical Devices Used For Decalcification

4.1 Angioplasty (Use Of Balloon)

The device comprises of a balloon attached to a catheter with its guidewire typically inserted through the femoral artery to the target site within a coronary or peripheral blood vessel. This is used to expand the cross-sectional area of the lumen of a vessel by compressing the calcified plaque outwards against the wall and inner linings of the vessel. Unfortunately, it would not be able to expand to the required size if the layer(s) of calcified plaque is too thick or too stiff. The vessel wall may also elastically rebound and collapse back. Drug-eluted balloon might also be used to accelerate healing of the inner wall of the vessel stretched or injured by the cross-sectional expansion to minimize the possibility of rebound collapse.

4.2 Stenting

A stent could be placed during angioplasty to maintain rigidity and stiffness of the expanded cross-section to avoid the rebound collapse of the vessel wall. Various types of stents, such as bare-metal stent, nitinol (self-expanding) stent, and drug-eluted stent, have been used. As in the case of drug-eluted balloon, the drug-eluted stent serves to heal the stretched and torn tissue of the vessel wall for up to 30 days and hold the expanded stent at its desired cross-sectional size. After healing of the tissue of the inner wall of the vessel is completed, the stent would retain its desired cross-sectional size. One problem with stents is that they may not achieve the required expanded cross-sectional size due to layer(s) of calcified plaque which are too thick or too stiff. One huge hurdle in the use of stent is the presence of calcified plaque deposited within the lumen of the blood vessel.

4.3 Atherectomy

The atherectomy process involves either cutting with a blade or grinding with a burr to remove calcified plaque within the lumen of a blood vessel. Care needs to be taken not to injure and cause trauma to the tunica intima and tunica media of the vessel wall. The main limitation of this method is that the deeper layers of calcified plaque between the tunica intima and tunica media and even between the tunica media and tunica externa cannot be reached without destroying or dissecting the vessel wall.

4.3.1 Cutting Balloon And Scoring Balloon

A cutting balloon has three or four small cutting blades or microtomes which can cut away bits of the calcified plaque within the lumen. A scoring balloon has helical scoring wires instead of blades which can crack the plaque in addition to cutting the plaque. The scoring balloon is deemed safer than the cutting balloon because there is lower risk of dissecting the vessel. The radial extent of the cutting blades or scoring wires can be increased by further inflating the balloon. This is an inherently slow process due to the small cutting area afforded by the thin cutting tip on each blade or scoring wire.

4.3.2 Laser Atherectomy

Here, high-energy is generated by a laser attached to the tip of the catheter to vaporize the calcified plaque up front of the laser. However, this process is time-consuming due to the required slow advance speed of the catheter.

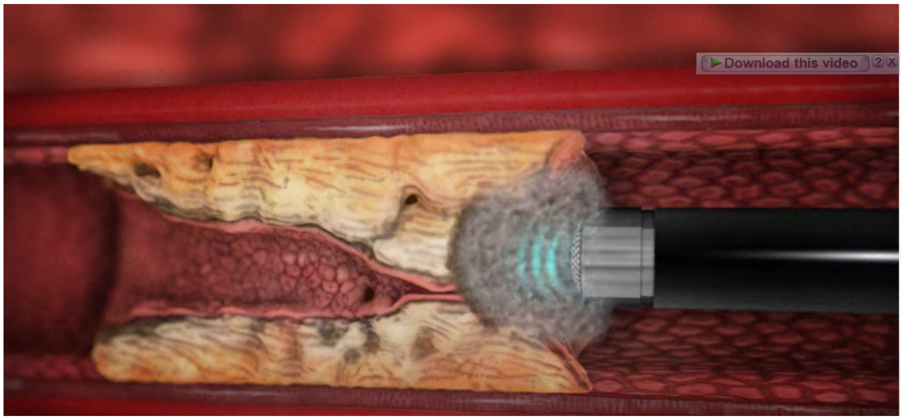


Figure 3: Laser atherectomy [4].

4.3.3 Directional Atherectomy

This is a much quicker technique using high-speed cutting blade encased in a cylindrical protective shell. The powdered plaque residues are collected up front by a receptacle.

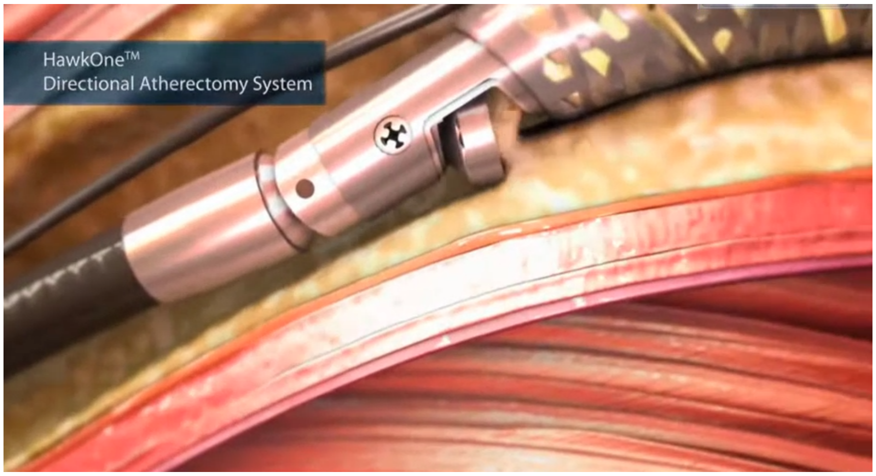


Figure 4: Directional atherectomy [4].

4.3.4 Rotational Atherectomy

Rotational atherectomy was developed about the same time as directional atherectomy but has become the favored and more commonly used technique for removing calcified plaque within the lumen of a vessel. It uses a grinding burr to remove the plaque. It grinds across a larger cross-sectional surface of the plaque and is therefore much quicker than directional atherectomy. However, like other atherectomy methods, it cannot treat large arteries like the left anterior descending artery (LAD). This is because a suitably large burr would not be able to pass along the femoral artery, which has a much smaller diameter than the LAD. The LAD is the largest coronary artery and is also the most common artery which is blocked by calcified plaque.

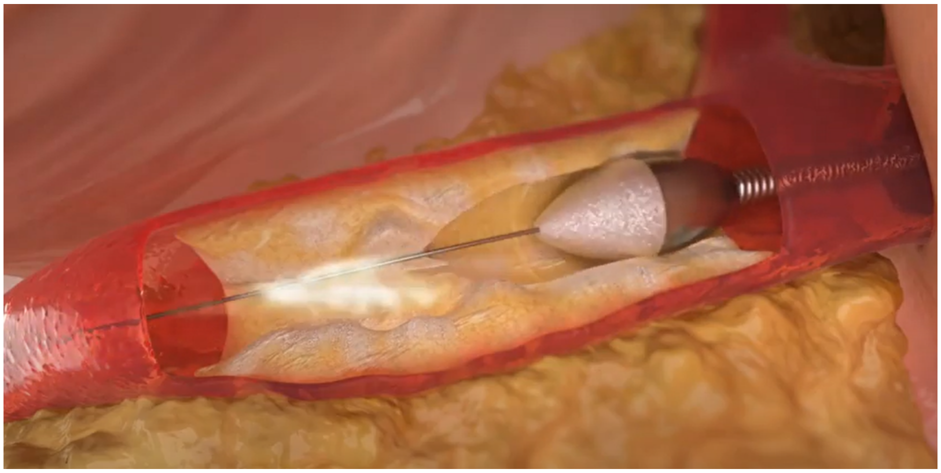


Figure 5: Rotational atherectomy [4].

4.3.5 Orbital Atherectomy

This is the only atherectomy technique which can remove calcified plaque from arteries which have diameters that are larger than those of the femoral artery. This is because of its unique system where the burr orbits about the central axis of the main guidewire. The orbit radius can be increased to remove plaque at radii that are greater than those of the femoral artery. However, like all other atherectomy techniques, it cannot remove plaque in deeper layers of the vessel wall. This problem could now be resolved with the use of a recently-developed technique called shockwave intravascular lithotripsy (IVL).

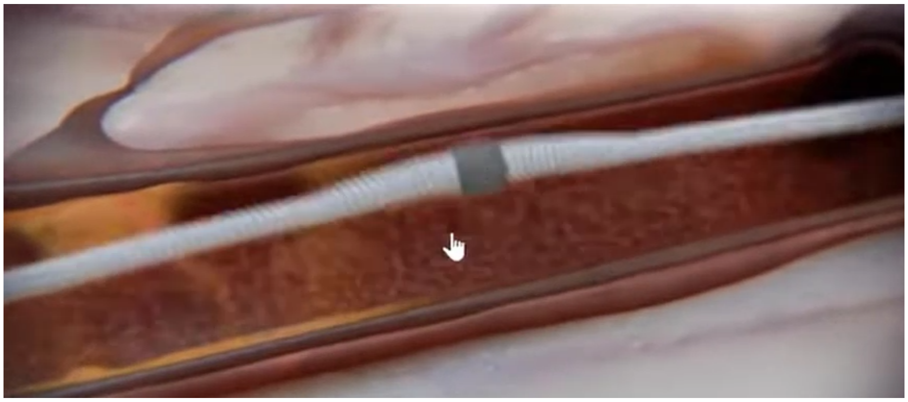


Figure 6: Orbital atherectomy [4].

4.4 Shockwave Intravascular Lithotripsy (IVL)

The Shockwave IVL device is delivered to the target site within the affected artery in the same way as angioplasty. The main difference is the acoustic shockwave emitters placed within the balloon to induce fissures and cracks within the calcified plaque. This significantly reduces the stiffness of the calcified mass thereby allowing the balloon to be inflated further by the operator to compress the broken-up plaque which subsequently allows for greater expansion of the stent to be placed.

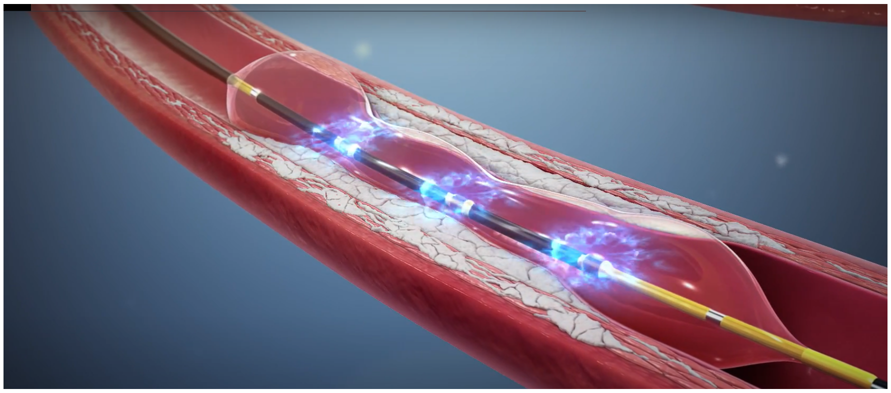


Figure 7: Shockwave intravascular lithotripsy (IVL) [4].

5 State-Of-The-Art Treatment Using Shockwave IVL

As mentioned above, calcification of coronary and peripheral arteries pose many problems and challenges in the treatment of several human diseases, some of which are fatal. About 40% of the cases treated with conventional methods such as stenting had failed because of the rigidity and toughness of the calcified plaque until the advent of a technique called shockwave intravascular lithotripsy (IVL). In the past five years, IVL have been tried and tested and recently approved by FDA for clinical use to break-up and compress calcified plaque in the affected vasculature. The complete system by Shockwave Medical, Inc. is shown in Figure 8-1. The technology is adapted from extracoporeal shockwave therapy (ESWT) for the removal of kidney stones. There are significant design adaptatons for its use in the treatment of coronary and peripheral calcification. First is the generation of a much lower intensity shockwave (see Figure 8-2) so as to disintegrate the calcified mass without trauma or damage to the vessel. Second is the use of acoustic emitters within a contrast-filled balloon. There are two acoustic emitters in the case of coronary catheters called the C2 catheters, five acoustic emmiters in the case of peripheral vasculature between the heart and the knee, called the M5/M5 Plus catheters, and four acoustic emitters for the peripheral vasculature below the knee called the S4 catheter. The number of acoustic emmiters correspond with the typical extent of calcification along the length of the respective vasculature. Shockwaves generated by the acoustic emitters are sufficient to initiate fissures even within deep layers of the calcified mass by the following mechanisms: (i) squeezing, (ii) cavitation, (iii) fatigue, and (iv) spallation.

Figure 8-1: The shockwave IVL system setup [4].

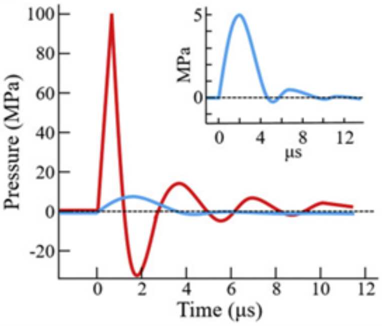


Figure 8-2: Characteristic low intensity shockwave in IVL (blue color) compared to high intensity shockwave in ESWT (red color). (Kereiakes. D.J., et al, 2021).

The shockwave IVL procedure is illustrated in Figure 8-3. Figure 8-3a shows a shockwave IVL catheter inserted into an affected segment of an artery where two light sources are seen indicating the two ends of the shockwave IVL balloon. Figure 8-3b shows the catheter comprising of contrast-filled balloon containing the acoustic emitters in place and surrounded by the calcified plaque segment of the blood vessel. As shown, the balloon has been inflated against the vessel wall up to a pressure of 4 atm. Here, the calcified plaque layers are sandwiched between the tunica intima and tunica media as well as between the tunica media and the tunica externa. Figure 8-3c shows the acoustic shockwaves being emitted in pulses to break-up the rigid and solid plaque. The shocks would cracked and loosen portions of the plaque thereby causing a drop in the balloon pressure. It would then be possible to further expand the balloon until 4 atm is reached again. The process is repeated for several iterations. When the balloon diameter reaches the desired size a final pressure of 5 atm is applied. Then, as shown in Figure 8-3d, the balloon pressure is released and the balloon collapses. The cross-section of the vessel typically remains enlarged with minimal rebound due to the crushed and compacted plaque particles. Following this, a stent may be placed.

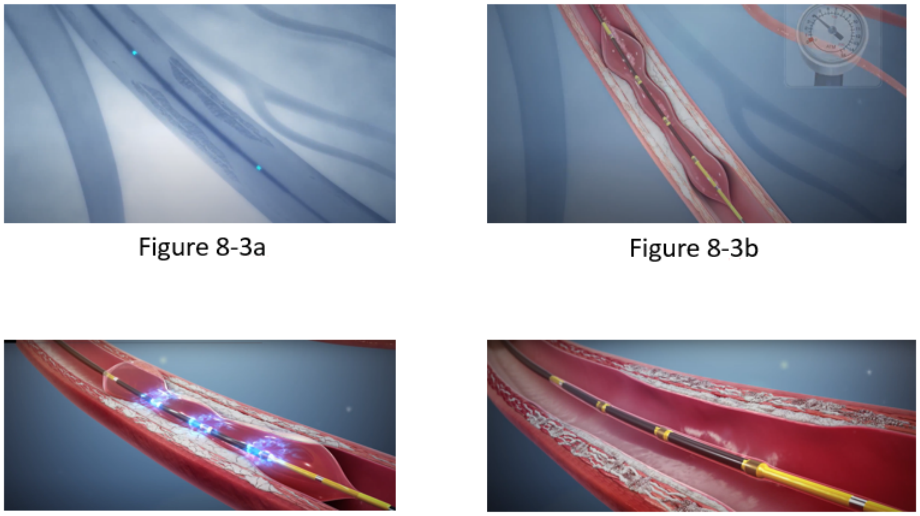


Figure 8-3a

Figure 8-3b

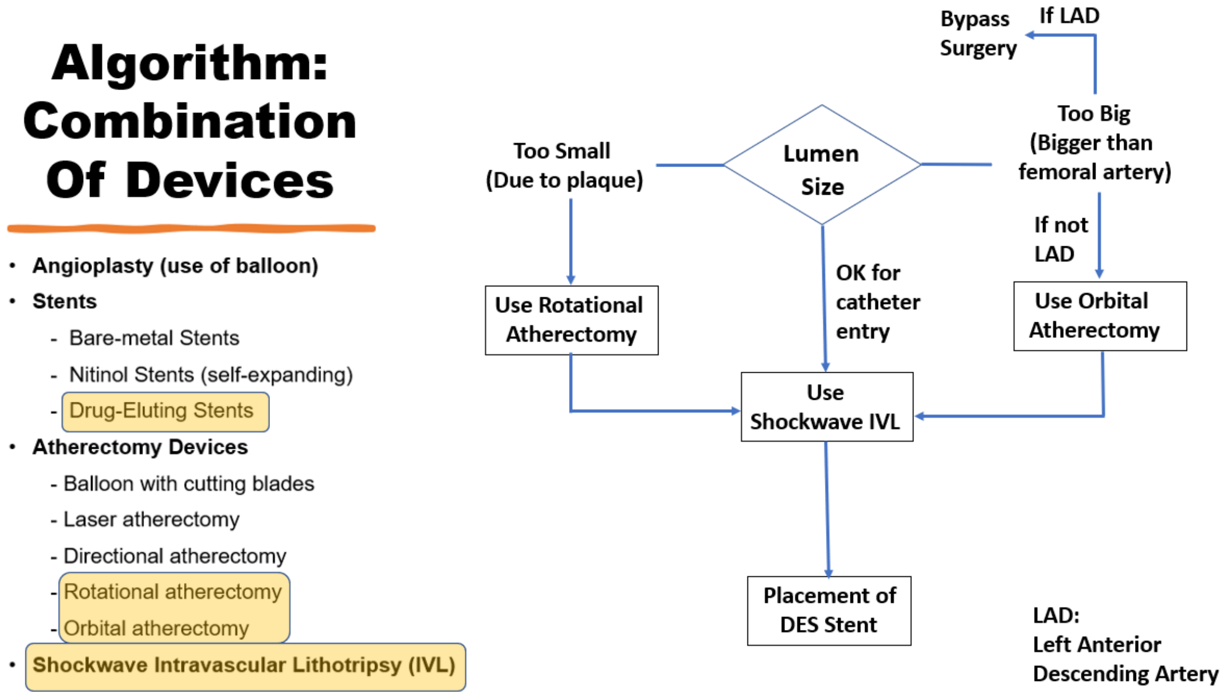
Figure 8-3c

Figure 8-3d

Figure 8-3: Stages of shockwave IVL

6 Algorithm For Device Selection

An algorithm is presented in Figure 9 for the selection of device and treatment method based on the unique features of each device. If the net lumen size of the segment of an affected artery permits the entry of the shockwave IVL catheter, then the use of shockwave IVL followed by the placement of a drug-eluting stent would suffice. If the net lumen size is too small due to calcified plaque accumulation within the lumen, then rotational atherectomy is recommended prior to the use of shockwave IVL and subsequent placement of the drug-eluting stent. However, if the net lumen size is bigger than the lumen size of the femoral artery and the vessel is not the left anterior descending artery (LAD), then orbital atherectomy would need to be used instead. This is because the grinding burr of the rotational atherectomy device would be too big to pass through the femoral artery. The LAD is also the largest coronary artery. And if the vessel is the LAD, then bypass surgery would most likely be required. Would it be possible that in future a device could be designed to replace the use of multiple devices and save time by reducing the number of procedures?



Algorithm: Combination Of Devices

- **Angioplasty (use of balloon)**
- **Stents**
  - Bare-metal Stents
  - Nitinol Stents (self-expanding)
  - Drug-Eluting Stents
- **Atherectomy Devices**
  - Balloon with cutting blades
  - Laser atherectomy
  - Directional atherectomy
  - Rotational atherectomy
  - Orbital atherectomy
- **Shockwave Intravascular Lithotripsy (IVL)**

Figure 9: Device And Treatment Method Selection Algorithm.

7 Safety And Efficacy Of Shockwave IVL

The Disrupt CAD III studies were carried out as the Phase 3 clinical trial for shockwave IVL. It was successfully completed in 2020 leading to the award of FDA's Pre-Market Approval in Aug 2020 [70]. It was carried out over a one-year period and demonstrated both safety and efficacy. The results indicated low rates of major adverse cardiovascular events (MACE) of just 13.8% and low rates of target lesion failure of only 11.9%. Optical Coherence Tomography (OCT) showed that shockwave IVL achieved an average stent expansion of 102%, which is up to 24% larger than with rotational atherectomy alone [71].

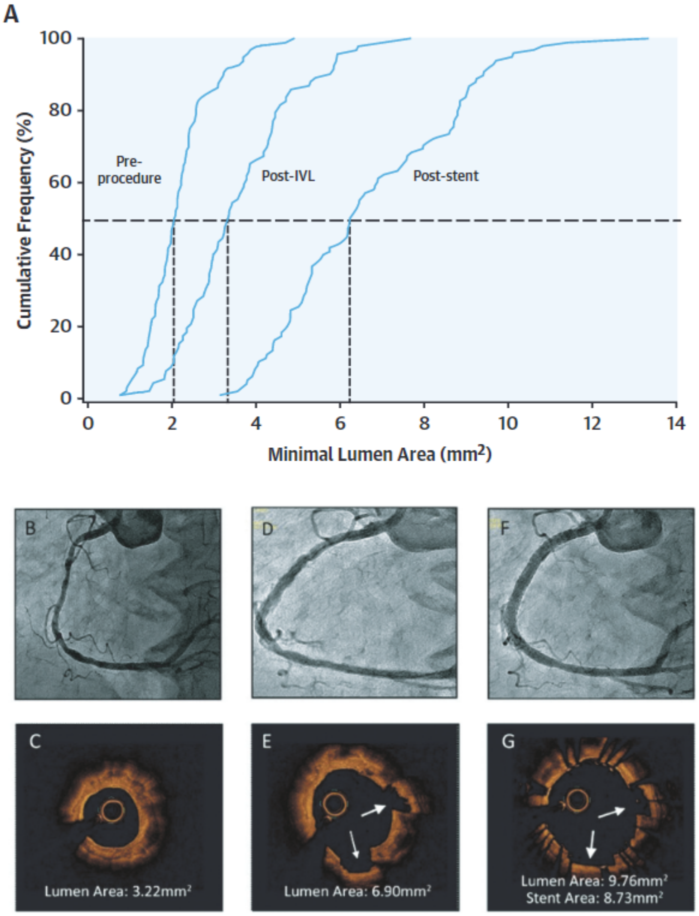


Figure 10: Some results of Disrupt CAD III.

8 Discussion: Public Health Perspectives

Currently, patients are not screened or tested to assess the degree of calcification in their arteries unless they experience an adverse cardiac event. They would either die of a heart attack or survive to be treated with the use of angioplasty and stenting, or if necessary using one of the atherectomy methods, or with bypass surgery. However, a preventive approach might be taken by adding a screening algorithm to the treatment algorithm based on the Calcium Score obtained through the use of a CT Scan as presented in Figure 11. An arbitrary screening age of 60 years and a treatment calcium score of 400 is suggested.

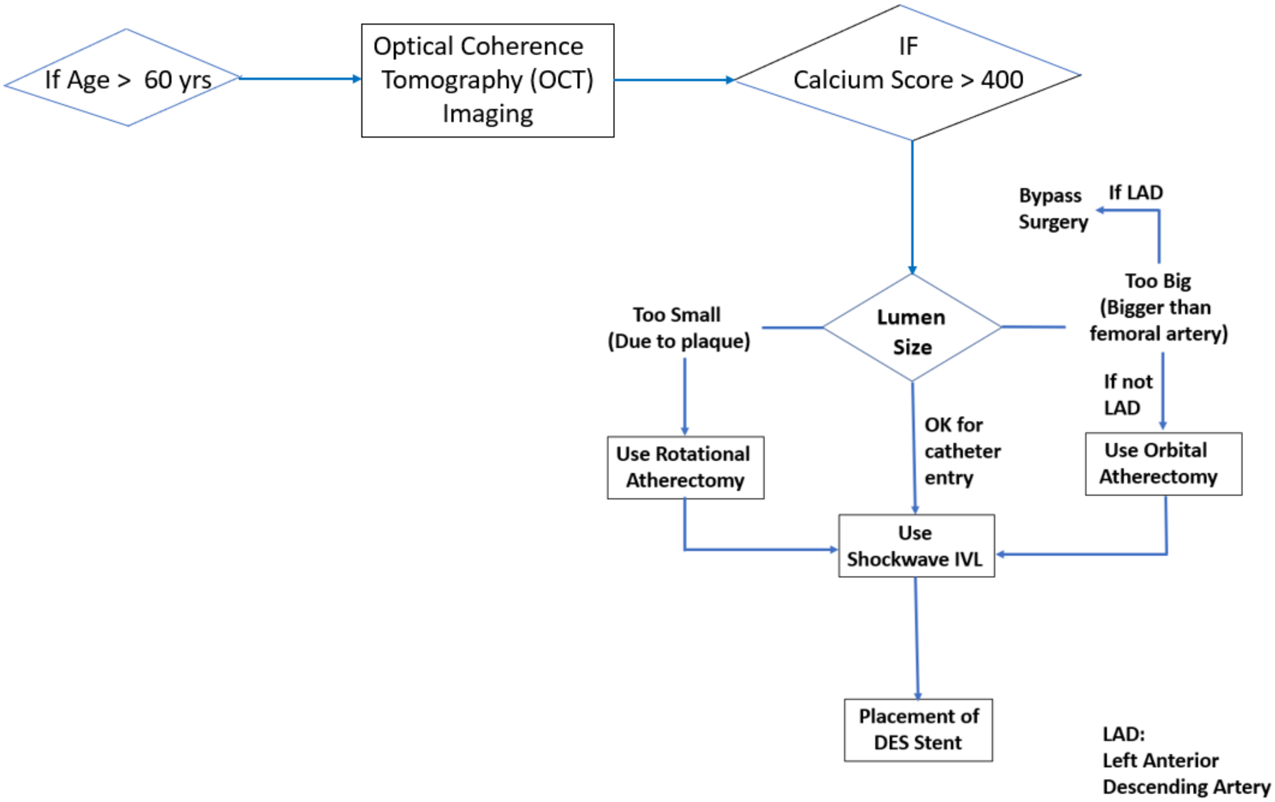


Figure 11: Combining Screening And Treatment Algorithms.

If the system could not cope with screening too many people or with treating too many people, the screening age may be adjusted higher. Or, if the system could cope with screening more people, the screening age could be lowered. And if the system could cope with treating more people, the treatment calcium score could be lowered. The number of incidence of heart attacks, number of bypass surgeries, and number of deaths due to cardiovascular diseases could be monitored and tracked in association with the screening age and treatment calcium score to ”optimize” the public health outcome and allocation of funding and resources (screening and treatment facilities, equipment and manpower). Different screening intervals may also be prescribed for each patient, depending on their age and calcium score.

A more conservative public health screening approach is to use an age-dependent and sex-dependent treatment calcium score defined as the calcium score above which 90% of people screened and found to have significant stenosis require treatment [80].

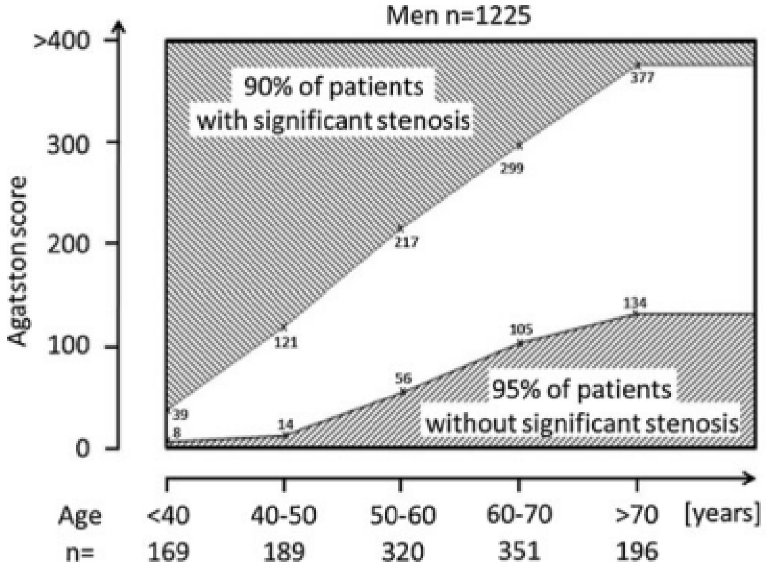


Figure 12a: Predictive calcium scores for significant coronary stenosis in men [80].

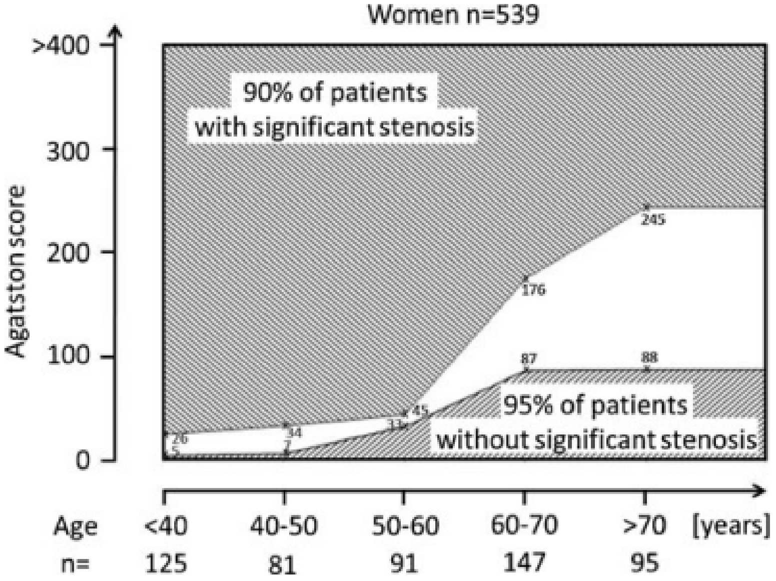


Figure 12b: Predictive calcium scores for significant coronary stenosis in women [80].

Based on the charts shown in Figures 12a and 12b, the treatment calcium score (TCS) may be defined as follows:

$$\text{For men, } \; \text{TCS} = \begin{cases} 10.0Age - 300 + \Delta_{m1} & \text{if } 40 \leq Age < 70 \\ 400 + \Delta_{m2} & \text{if } 70 \leq Age \end{cases}$$

$$\text{For women, } \; \text{TCS} = \begin{cases} 0.9Age - 15 + \Delta_{w1} & \text{if } 40 \leq Age < 50 \\ 13.1Age - 610 + \Delta_{w2} & \text{if } 50 \leq Age < 60 \\ 6.9Age - 238 + \Delta_{w3} & \text{if } 60 \leq Age < 70 \\ 245 + \Delta_{w4} & \text{if } 70 \leq Age \end{cases}$$

where $\Delta_{mi's}$ and $\Delta_{wj's}$ are discretionary constants which may be adjusted to balance the expected number of lives to be saved against the government's budget for a public health screening and treatment project. Treatment is provided to the patient when his/her calcium score exceeds the treatment calcium score. If there are no budget and resource constraints, all the discretionary constants may initially be set to zero. In this case, up to 90% of people screened and having significant stenosis could be saved.

9 Investment Potential Of A Biomedical Device

The successful completion of Phase 3 clinical trial called Disrupt CAD III for shockwave IVL and the FDA Pre-Market Approval obtained in August 2020 had a remarkable effect on the share price of Shockwave Medical Inc. (NASDAQ Stock Code: SWAV), as shown in Figure 13. Its share price has been increasing since then, as the popularity and use of shockwave IVL gains momentum. It would further rise if the US government becomes more concern about a cardiovascular disease epidemic and sees the need to save hundreds of thousands of human lives.

Figure 13: Investment potential of shockwave IVL.

10 Conclusion

The design, functional aspects, and limitations of the different types of biomedical devices used for treating coronary calcification were reviewed. A treatment algorithm combined with a screening algorithm is proposed to reduce the incidence of heart attacks and number of deaths due to cardiovascular diseases. Equations for treatment calcium scores have also been developed and proposed to guide public health initiatives and optimize outcomes and government budget allocation. Up to 90% of human lives screened and have significant stenosis could be saved. This paper demonstrated how thoughtful designs of biomedical devices can have a very crucial impact on human lives and how a variety of devices with their own unique design features can complement each other. However, further innovation is still possible to reduce the number of treatment procedures and treatment time.

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