Review

The Development of Carotid Stent Material

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Abstract
Endovascular angioplasty with stenting is a promising option for treating carotid artery stenosis. There exist a rapidly increasing number of different stent types with different materials. The bare-metal stent is the most commonly used stent with acceptable results, but it leaves us with the problems of thrombosis and restenosis. The drug-eluting stent is a breakthrough as it has the ability to reduce the restenosis rate, but the problem of late thrombosis still has to be addressed. The biodegradable stent disappears after having served its function. However, restenosis and degradation rates remain to be studied. In this article, we review every stent material with its characteristics, clinical results and complications and point out the standards of an ideal carotid stent.

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Introduction

Stroke is a serious medical and social problem. Ischemic stroke is one of the leading causes of death, and suffering a stroke is in 85% of all cases the reason for an acquired disability in adulthood. Stenosis of the carotid artery is one important etiological factor [1–3]. Endovascular angioplasty with stenting (CAS) has been found to be a promising option for treating carotid artery stenosis [4–7]. However, CAS is not a panacea for this disease; there are still complications associated with CAS [8, 9]. Among the many factors influencing CAS, the stent material plays an important part. In the history of the development of carotid stent material, every single material has its merits and drawbacks.

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Bare-Metal Stents

Bare-metal stents were the first generation of carotid stents. They helped relieve the decrease in luminal diameter after angioplasty effectively. However, every material has its specific characteristics.

Stainless Steel Stents

Within the family of stainless steel stents, the 316L stainless steel stent is the most common one. 316L stainless steel has been one of the first materials to be used in carotid stenting. It is composed of chromium, nickel, molybdenum, manganese, silicon, carbon, phosphorus, sulfur and iron [10]. Stainless steel can be used in both balloon-expandable and self-expanding stents. It can be easily deformed when in its fully annealed state, which is of key importance for balloon-expandable stents. On the other hand, it has enough elasticity when fully hardened to serve the concept of self-expanding stents. Stainless steel is a strong material with a high radio force; therefore it may prevent the abrupt closure of a vessel, in addition to having a good biocompatibility and being safe for the human body. It has been the gold standard for stents other materials [11].

Stainless steel stents have been used successfully in many cases. Mukherjee et al. [12] assessed 178 patients in their study. Of these 178 patients, 89 received stainless steel stents and 89 received nitinol stents. At 6 months' follow-up, there were no differences in the incidence of stroke (3.3 vs. 2.2%) between the stainless steel stent group and the nitinol stent group. However, the mortality rate of the stainless steel stent group was higher than that of the nitinol stent group, but there were no neurological deaths in either group. This proved that stainless steel stents are as safe as nitinol stents.

Having been the first material to be introduced to the field of stenting, stainless steel still causes many problems which need solving: they have a low MR compatibility, they are more likely to induce vessel wall injury [13] compared with nitinol stents, they have a low corrosion resistance and a bad vessel wall-stent apposition, and they release metal ions [14] inducing inflammatory and cell apoptosis. These issues need to be resolved.

Cobalt Alloy Stents

Cobalt alloy is another material used in carotid stents, usually in balloon-expandable stents. It is composed of cobalt, chromium and other metal elements. Compared with 316L stainless steel, cobalt alloy is stronger and has a higher radio-opacity. These properties make thinner stent struts possible [15]. Thinner struts, on the other hand, make the device more flexible and reduce the stent's cross-sectional diameter. Additionally, thinner struts have been proven to lead to a reduced restenosis rate. With their inherent corrosion resistance, acceptable vessel wall-stent apposition [16] and good biocompatible properties, cobalt alloy stents acquired a more and more important role in CAS.

Vajda et al. [17] analyzed 25 patients (30 lesions) in their study, using balloon-expandable cobalt chromium stents (Coroflex Blue). All procedures were successful. As many as 29 out of the 30 lesions (97%) met the standard of residual stenosis of <50%. Of the 30 procedures, 28 were uneventful; however, the CAS led to 1 transient and 1 permanent neurological deficit in the remaining 2 cases. All patients were followed up with an angiogram after a median of 15.2 months. There, the authors noted a recurrent stenosis rate of 11 out of 30 lesions, which is a significant problem. In summary, cobalt alloy stents are safe and feasible to be used in carotid stenting, but the restenosis rate remains a concern.

With an increasing number of cases being reported, the safety, feasibility and complications after using cobalt alloy stents will need to be further analyzed in CAS in the future.

Nitinol Stents

Nitinol is an alloy composed mostly of nickel-titanium as well as cobalt and other metal elements. Nitinol alloy is the material most commonly used in carotid stents nowadays, usually for self-expanding stents. Self-expanding nitinol stents are usually manufactured slightly larger than the size of the target vessel. After deployment, this results in a small, 'chronic'/constant outward force against the recoil pressure between the stent and the vessel wall. Nitinol stents have a high radial-resistive force against outside compression [18].

Nitinol stents have 2 unique merits: superelasticity and shape-memory properties [19]. The elastic deformation of stainless steel and cobalt alloys is limited to approximately 1% strain. Nitinol, on the other hand, can be elastically deformed up to about 10% strain in some cases. After being released, the elastic deformation can be fully recovered. That property is called superelasticity, thus providing nitinol stents with a better vessel wall-stent apposition. On the other hand, when stress is applied to a nitinol stent, it deforms/bends temporarily, adapting to a changing situation. Once the stress is released, the material recovers its original structure and shape. This property is called shape memory.

Compared with 316L stainless steel balloon-expandable stents, the nitinol self-expanding stents have a much lower elasticity and a remarkably higher yield to stress. A titanium-oxide layer can passively form on the surface of nitinol stents, making them corrosion resistant [20]. This adds to nitinol stents having a better biocompatibility than 316L stainless steel stents. In addition, nitinol produces fewer artifacts than stainless steel and reproduces better on MR images.

Nitinol stents have been successfully used in clinical practice. Phatouros et al. [21] and Drescher et al. [22] have used nitinol self-expanding (SMART) stents in the treatment of 4 and 13 patients, respectively. In Phatouros et al.'s cases, all procedures were successful (<20% residual stenosis). There were no SMART stent-related complications. During the 6-month follow-up period, no transient ischemic attacks or new strokes took place, which means the patients remained symptom free. This shows that SMART stents are safe and feasible. In Drescher et al.'s cases, the stenosis was successfully reduced to an average of 2.8% (0–21). However, restenosis was found in 8 out of the 13 patients during the 6-month follow-up period. Apart from that, 1 patient experienced brief neurological symptoms during the intervention. No further complications occurred during follow-up. These cases also show that SMART stents are safe and feasible to use for treating carotid stenosis, but also that restenosis is a big problem to address. In another multicenter study, Qureshi et al. [23] analyzed 71 patients (73 lesions). Only 4 procedures were unsuccessful. The residual stenosis was reduced significantly in the other 69 lesions treated with nitinol Bard Memotherm stents. A total of 65 (89%) of the 73 procedures meet the primary endpoint. One major ischemic stroke was found in 1 patient, and another patient died of intracerebral hemorrhage. The overall 1-month stroke rate was 2.7% for the 73 attempted procedures. This shows that Bard Memotherm stents can be used in the treatment of patients with coronary artery stenosis and are associated with a low peri-procedural complication rate.

However, nitinol stents also have some drawbacks, e.g. a weak radial-resistive force compared with 316L stainless steel stents, a low radio-opacity and a liability to fracture. Due to modifications to the surface [24] and other techniques, these drawbacks will soon be overcome. Additionally, a new stent design will lead to improvements in the radial-resistive force and other properties [25]. Markers like gold or tantalum are attached or integrated into the design of the stent to improve radio-opacity. With more and more techniques making use of this material, there will be a brighter tomorrow for nitinol stents.

Although a high initial success rate has been achieved with bare-metal stents, early and late complications including (sub)acute occlusion and neointimal hyperplasia resulting in the in-stent recurrence of stenosis (in-stent restenosis) is something that cannot be ignored. Researchers are working on strategies focused on these complications.

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Coated Stents

Coated stents are composed of a kind of stent material, usually bare metal, coated with another material on the surface. The coating material can be divided into passive and active coating [26]. Passive coating is based on gold, carbon, a polymer or ceramic coating. Active coating usually includes drugs, e.g. heparin or recombinant human thrombomodulin, which can interfere with the process of thrombosis and neointimal hyperplasia. Some believe that the coating can reduce metal ion release, neointimal hyperplasia, surface thrombogenicity and platelet activation and thus improve biocompatibility.

Unfortunately, the clinical results of coronary artery stenting could not always confirm its theoretical advantages [27]. The rates of thrombus formation and restenosis of coated stents were either higher than or equal to those of bare-metal stents. There are only animal data about coated stents used for carotid arteries. Some of the results are promising and some are not [28, 29]. Maybe the passively coated stent (no drugs) is not ideal as carotid stent material.

Radioactive Stents

Radiotherapy has been proved to be successful in clinical experience to prevent in-stent restenosis of the carotid artery [30–32]. In Pokrajac et al.'s study [31], radiotherapy was given to 5 patients after carotid artery angioplasty. No acute side effects associated with radiotherapy were observed, which means all patients tolerated the treatment well. During the 4-month follow-up period, 2 patients were found with recurrence of stenosis. However, late total occlusion of the stent was noticed in all cases. Three patients remained symptom free with <50% restenosis, 1 patient developed a severe stroke and the last patient died. This shows that radiotherapy is a feasible treatment option for highly selected patients with carotid artery in-stent restenosis. However, the application of radioactive stents has only been reported in animal carotid experiments [33], which showed promising results in suppressing neointimal formation.

One clinical trial attempted applying radioactive stents to coronary artery stenosis [34]; the results showed that in-stent neointimal hyperplasia was reduced in a dose-dependent manner. However, the rate of intralesional restenosis was high because of late lumen loss in the reference segments at the edges of the stents, called the candy wrapper effect.

Even though the future of radioactive stents is promising, due to the risk of late thrombosis and the candy wrapper effect, there is much work to be done before a clinical application of radioactive stents in carotid arteries is feasible.

Drug-Eluting Stents

The emergence of drug-eluting stents (DES) is a milestone in the history of stent development. There is hope to eliminate in-stent restenosis with DES. DES are stents bonding with drugs that are then constantly released to surrounding tissue. The difference between DES and drug-coated stents is that the drugs of DES can be constantly released to surrounding tissue. DES are composed of 3 basic parts: the bare metal, the drug delivery system and the drugs. There are 3 generations of DES on the market today [35]. The first-generation DES are made from a bare metal stent and a permanent polymer coating that has limited flexibility and is fairly plain. The second-generation DES are composed of durable coatings, which make them more biocompatible than first-generation DES. The third-generation DES show a strong

focus on design and material, which makes them more flexible and highly deliverable. Some studies have experienced clinical success with DES in the carotid artery [36, 37]; the results showed that this generation of DES can effectively diminish restenosis rates.

The drugs within the DES should be effective but not toxic. The two most commonly used drugs are sirolimus and paclitaxel. Sirolimus is an immunosuppressive agent. It works by interacting with a specific target protein (mTOR, the mammalian target of rapamycin) and inhibiting its activation to block the G1-to-S cell cycle progression. The inhibition of mTOR suppresses cell proliferation. Sirolimus has also been reported to prevent neointimal formation through MAPK and NF-κB pathways [38]. In animal experiments, sirolimus-eluting stents reduced neointima significantly (5.9 ± 2.5 vs. 0.7 ± 1.0 mm^2) compared with bare-metal stents [39]. This proves that sirolimus is effective in inhibiting neointimal formation. Paclitaxel is an antiproliferative agent. Pharmacologically, its effect is to allow the generation of numerous decentralized and unorganized microtubules. Thus, an assembly of extraordinarily stable microtubules will be enhanced, which interrupts proliferation, migration and signal transduction and can induce apoptotic cell death in a number of cell types [40]. In animal models, the neointimal area, the area of stenosis and the maximal neointimal thickness were significantly lower using paclitaxel-eluting stents than with referential bare-metal stents [41]. This shows that paclitaxel-eluting stents inhibit neointimal formation effectively.

Other candidate drugs for DES are zotarolimus, tacrolimus and fludarabine [42–44]. Dual DES (1 stent, 2 drugs) have been reported to reduce thrombosis and proliferation at the same time [45]. There are also studies of gene vector delivery for gene therapy based on this platform [46]. Both studies indicate a promising future for DES. Nevertheless, the possibility of late thrombosis, related to delayed re-endothelialization, has to be considered. Ma et al. [47] reported that the process of re-endothelialization could be ameliorated by glycogen synthase kinase-3β inhibitor treatment via enhancing the adhesion of endothelial progenitor cells. There will most certainly be more studies focusing on this problem in order to eliminate this Achilles' heel.

However, so far, clinical studies applying DES to the carotid artery are lacking. Further randomized studies are needed to examine the effectiveness, safety and complications of these devices.

DES mark a major step forward in the development of carotid stents. But as they are permanent devices in the body, there are still complications associated with them. These considerations drove researchers to find a material more compatible with the human body.

Biodegradable Stents

Although stents have been successfully used in the treatment of carotid stenosis, there are still some limitations to stents which remain to be resolved. The limitations of metallic stents are an impairment of the vessel's geometry, a mismatch of the stent to the vessel size and stent thrombosis, which requires prolonged antiplatelet therapy. DES are a breakthrough in the development of stents because of their ability to significantly reduce restenosis rates. But the possibility of subacute and late thrombosis associated with them is another problem to be addressed. Apart from that, permanent devices staying in the body can hinder future surgery or revascularization and can cause rejection at any time. However, biodegradable stents disappear within a limited time, and once biodegraded, a healed natural vessel with a chance of restoration of vasoreactivity will be achieved, including the potential of vessel remodeling. In that moment, patients will no longer have to worry about late stent thrombosis and will no longer need prolonged antiplatelet therapy, since the stent is gone [48].

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Polymer Stents

Polymer stents are the first type of biodegradable stents ever used. The first polymer proposed for a biodegradable stent was poly-L-lactic acid (PLLA). Other polymers that have been suggested are polyglycolic acid, polycaprolactone and poly(D,L-lactide/glycolide) copolymer [49, 50]. There have been clinical trials using biodegradable polymeric stents in the coronary artery showing their effectiveness and safety. However, so far there have only been animal experiments with polymeric stents in the carotid artery. Kischkel et al. [51] implanted a novel biodegradable stent based on PLLA and poly-4-hydroxybutyrate into the porcine carotid artery. Their PLLA/poly-4-hydrocybutyrate stent group showed a decreased residual luminal area and higher restenosis but a lower vascular injury score than the 316L stainless steel reference group, which means the novel stents have a good biocompatibility but the high restenosis rates are a serious problem.

There are still limitations to polymer stents, e.g. their lower strength compared to metallic stents, local inflammation and restenosis rates [48, 49]. Further studies are needed to resolve these limitations.

Magnesium Alloy Stents

Magnesium is the fourth most plentiful cation in the body, and people have studied its biological role extensively. The concentration of magnesium released from a stent is extremely low compared to the physiological magnesium content in the plasma (0.70–1.05 mmol/l). A magnesium alloy is expected to satisfy most requirements of a biodegradable vascular stent, such as mechanical properties, biocompatibility and degradation/absorption performance. In a prospective, multicenter, clinical trial, magnesium stents have been implanted into 63 patients with de novo coronary lesions [52]. An immediate angiographic result similar to that of other metal stents was achieved, and the stents were safely degraded after 4 months. However, the degradation rate was higher than expected. Lu et al. [53] controlled the corrosion resistance and the biodegradation rate by fabricating a micro-arc oxidation/PLLA coating on the magnesium alloy AZ81 substrate. Another study showed that by the addition of alloying elements, especially rare earth elements and other metallic elements including calcium, lithium and zirconium, the mechanical properties and corrosion resistance of magnesium alloys can be improved [54]. However, there are no studies on the application of magnesium alloy stents to the carotid artery.

Iron Alloy Stents

Iron is another essential element in the human body, meaning a release of iron ions from stents is not toxic to surrounding tissue. Iron alloy (Fe-based alloy) stents have a high radial strength because of their higher elasticity. This can be helpful when making stents with thinner struts. The first iron stents produced from pure iron were implanted into the native descending aorta of 16 New Zealand white rabbits [55]. This resulted in no thromboembolic complications, no pronounced inflammatory response, no significant neointimal proliferation and no systemic toxicity. Wu et al. [56] implanted iron stents into mini-swine coronary arteries. As a result, the mean neointimal thickness, neointimal area, percentage of area stenosis and intimal injury scores were not significantly different between the iron stents and the cobalt chromium reference stents. Those studies showed that iron-based stents have a good biocompatibility and short-term safety and efficacy. But the low degradation rate is a big problem. In Huang et al.'s study [57], iron-5 wt% palladium and iron-5 wt% platinum composites were tested. The results showed that the degradation rates of the iron-palladium and the iron-platinum composites were much faster than that of pure iron. Another study showed that microstructural modifications can change the degradation rate [54]. Once the degradation rate is appropriate, iron alloy stents will be perfect biodegradable stents. Nevertheless, there have been no studies on iron alloy stents in the carotid artery so far.

The Aim

The ideal biodegradable stent should: (1) be biocompatible, and the degradation products of the material must also be biocompatible; (2) stay in place for 6–12 months before it is completely biodegraded and still have enough radial force for a scaffolding effect during the requested period, and (3) have ideal degradation rates, be completely degraded after 6–12 months, allowing positive artery remodeling [58]. Today, no available stent meets these standards. When the limitations of polymers and the degradation rates of magnesium and iron are 'solved problems', these biodegradable stents will most likely be ideal stents.

Even though there have only been animal experiments with polymer stents in the carotid artery so far [51, 59], biodegradable stents will be the ideal stents in the future considering the advantages they have. We need more studies to analyze the safety, feasibility and limitations of biodegradable stents in the carotid artery before their clinical application.

Stent Design

There is also the aspect of stent design. Stents can be divided into balloon-expandable and self-expanding stents; the characteristics have been described previously. The raw material includes sheets, wires and tubes. Stents can be fabricated by coiling, braiding, knitting, laser cutting or water-jet cutting. Meanwhile, photochemical etching is another new method for stent fabrication. The geometry of stents includes coils and helical spirals as well as woven, individual and sequential rings. In detail, open-cell and closed-cell stents are subcategories of sequential rings. Open-cell stents describe constructions where none or only some of the internal inflection points of the structural members are connected by bridging elements. In contrast, closed-cell stents are of the kind that all internal inflection points of the structural members are connected by bridging elements [11, 60].

Based on different aspects of design, stents will have different performances. For example, a heat-affected zone along the cut edge will show up in laser-cut products but not in water-jet-cut products. Both coil stents and helical-spiral stents are extremely flexible, but coil stents are high-profile devices, while helical-spiral stents show a lack in longitudinal support. Woven stents offer excellent coverage, but they shrink during expansion. Open-cell stents are more flexible than closed-cell ones; however, closed-cell stents have an optimal scaffolding property and a uniform surface, regardless of the degree of bending.

Apart from their different performance based on engineering, stents with different designs result in different clinical features [11]. Neointimal hyperplasia can be influenced by stent design, as has been shown in animal models. Different vessels and lesions need different stents. Tortuous lesions require particularly flexible and conformable stents. Stents with strong radial support and good radiological visibility are needed in ostial lesions. Bifurcational lesions need stents with large side openings that permit the passage of a second stent or a balloon, and small vessels prefer flexible stents with a thin strut structure. There are also studies showing that different stent designs can influence the wall-rheological characteristics, hemodynamic performance, degree of platelet activation [61] and stent thrombosis. Numerous trials have shown that tubular and multicellular stents produce better results than wire mesh and coil stents concerning thrombosis and restenosis in the coronary artery [62–64]. There are also other trials on stenting the coronary artery which proved that there are more vascular injuries, more intimal hyperplasia and a higher risk for restenosis using stents with thicker struts than thinner struts [65–67].

The material, raw material forms, fabrication methods and geometry are all important aspects of stent design. They can influence clinical results in different ways. Only when all of them are considered properly, stents suitable for clinical use can be manufactured.

Table 1. The characteristics of the stent materials reviewed

	Merits	Drawbacks	Application proofs
Bare-metal stents			
Stainless steel	high strength and radio force, good biocompatibility	low MR compatibility, low corrosion resistance, bad vessel wall-stent apposition	clinical data
Cobalt alloy	high strength and radio-opacity, good corrosion resistance, biocompatibility	restenosis	clinical data
Nitinol	superelasticity and shape memory property, biocompatibility	weak radial-resistive force, low radio-opacity, fracture	clinical data
Radioactive stents	prevent restenosis	candy wrapper effect, late thrombosis	animal experiment data
Drug-eluting stents	reduce restenosis rate	late thrombosis, stay permanently in the body	clinical data
Biodegradable stents			
Polymer(s)	disappear after several months	lower strength, local inflammation, restenosis	animal experiment data
Magnesium alloy	disappear after several months	degrade too fast	no data on carotid artery
Iron alloy	disappear after several months	degrade too slowly	no data on carotid artery

Future Perspectives

Bare-metal stents have a decent scaffolding strength and can prevent early vessel recoil, but they may result in thrombosis and restenosis. DES are a breakthrough in the development of stents because of their ability to significantly reduce restenosis rates. However, the subacute and late thrombosis rates associated with them are a problem to be addressed. Biodegradable stents disappear after they have served their function, and this seems to be the ideal option for stent development. However, the biodegradable polymers have unacceptable restenosis rates, and the degradation rates of biodegradable metal stents remain to be studied. The characteristics of every material are showed in table 1.

There have been reports of a hybrid stent, which is a combination of a biodegradable stent and a DES [68–71]. These stents are antiproliferative, have an anticoagulative effect and are anti-inflammatory; additionally, they disappear after having fulfilled their purpose. These stents have the potential to be ideal stents.

The ideal stent should (1) have a good biocompatibility and be nontoxic to the body, (2) be able to cure the carotid stenosis effectively and (3) result in no complications and not hinder surgery or other operations in the future [11]. There is no stent today that could cover all of these aspects. Looking at studies coming up now, we have good reason to believe that there will be a perfect material for an ideal stent in the future, which will cure more patients and give them a better life.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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