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Approaches to antithrombotic modification of vascular implants

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Abstract

Vascular implants in contact with blood must have high thrombotic resistance. However, in some cases, their implantation is associated with thrombosis and subsequent impaired patency of the blood vessel. Most often, this problem affects implants intended for reconstruction of small diameter vessels, which is associated with hemodynamic features in this part of the bloodstream. These include blood vessel prostheses, tissue-engineered vascular grafts, and endovascular stents. The features of the implant material are of great importance when choosing a method for its modification in order to improve biocompatibility and thromboresistance. The review analyzes current experience in using various methods of immobilizing drugs to the surface of vascular prostheses and endovascular stents made from stable and biodegradable polymers. The prospects of creating thromboresistant vascular grafts and stents by joint immobilization on the surface of the polymer material of drugs with antithrombogenic activity and biologically active molecules that regulate the reaction to a foreign body and implant remodeling were evaluated. Numerous studies in the review demonstrating a wide range of ways to modify blood vessel prostheses, tissue-engineered vascular grafts, and endovascular stents with antithrombotic drugs to increase their thrombosis resistance. The main approaches of antithrombotic modification include conjugation of drugs and biologically active molecules on the implant surface. At the same time, new technologies are aimed not only at inhibiting the process of thrombus formation, but also at reducing the intensity of the inflammation process and stimulating the reparation of vascular tissue.

Keywords: vascular prostheses, vascular grafts, endovascular stents, anticoagulants, antiplatelet agents, thromboresistance, biodegradable polymers.

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Stenosis and occlusion of blood vessels are associated with or cause several cardiovascular diseases and pathological conditions, for instance, coronary heart disease, cerebrovascular accident, and internal vein thrombosis [1]. Surgical treatment of these conditions consists of replacing a damaged blood vessel with an autologous vein or artery, or a prosthesis [1]. In some cases, the vessel lumen can be restored using minimally invasive procedures, namely by balloon dilatation and stent placement [2]. In situations requiring replacement of a blood vessel, autologous vessels are the gold standard of the implant; however, due to atherosclerotic damage or previous surgery to the vessel, this option may be unavailable [1].

Synthetic vascular prostheses made of polyethylene terephthalate (PET, Dacron) and polytetrafluoroethylene (PTFE, Teflon) serve as an alternative to autovein and autoarteria [3]. These prostheses demonstrate high efficiency in large vessels with an inner diameter of more than 6 mm. The high blood flow velocity in large vessels and the relatively inert properties and strength of PTFE, and PET contribute to maintaining patency and wall integrity of these synthetic implants under high pressure. Vascular prostheses of small diameter (<6 mm) made of PTFE and PET are highly prone to thrombosis, which is due to the low blood flow velocity in these vessels and the compliance in conformity of the implant material and compliance of the blood vessel tissues, which also causes neointimal hyperplasia in the zone anastomosis followed by vascular stenosis [3].

An alternative type of vascular prosthesis that is currently beginning to demonstrate positive and promising results in clinical trials is tissue-engi-

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neered vascular grafts [4]. Significant progress in the field of vascular tissue engineering has enabled us to obtain a small-diameter vascular graft that has the necessary mechanical properties, imitates the extracellular matrix structure, and can be remodeled to form blood vessel tissues with the involvement of body cells. However, implant remodeling and endothelial formation are time-consuming; therefore, graft material that comes into contact with blood should also have a high thrombotic resistance [5].

When restoring the lumen of blood vessels with minimally invasive surgical methods, stents based on biocompatible metals and/or polymers are used, which are delivered to stenosed vessels through a small opening in the femoral artery [2]. Endovascular stents should have an ultra-thin wall thickness, mechanical strength, and a surface with anti-thrombotic properties.

One of the primary requirements for all vascular implants is high hemocompatibility, including thrombotic resistance. There are currently three main strategies used to increase thrombotic resistance of surfaces in contact with blood. These include the creation of a bioactive surface using anti-thrombotic agents; treating the implant surface with passivation using hydrophilic and zwitterionic polymers, which in turn prevents contact of the primary material of the product with blood and prevents non-specific adhesion of the protein; as well as endothelialization of the internal implant surface [5–7]. The creation of the endothelial layer is required mainly in the development of tissue-engineered vascular grafts, while the first two strategies are applicable in the modification of all types of vascular implants.

This article discusses the main approaches to surface modification of vascular prostheses, stents, and tissue-engineered vascular grafts using anti-thrombotic drugs and biocompatible polymers.

Anti-thrombotic drugs used to modify the implant surface. Anti-thrombotic agents, such as anticoagulants and antiplatelets, which are immobilized on the product surface, are widely used to increase the hemocompatibility of implants in contact with the blood. Anticoagulants represent a group of drugs that inhibit the activity of the blood coagulation system and prevent blood clot formation.

Heparin is the most used anti-thrombotic agent for the modification of vascular implants and tissue-engineered vascular grafts. It is a direct-acting anticoagulant, endogenous sulfated glycosaminoglycan, which is contained in mast cells [8]. The anticoagulant effect of heparin is due to its binding to antithrombin III, which inhibits activated coagulation factors, in particular thrombin (factor II), Xa, XIIa, and IXa. The binding of heparin to antithrombin III causes conformational changes that open the reactive site of antithrombin III, increasing its ability to inhibit blood coagulation factors [9, 10]. Additionally, heparin interacts with a large number of growth factors that have a heparin-binding domain. Delivery systems based on this anticoagulant can prevent the enzymatic degradation of related growth factors, thereby enhancing their biological functions [11].

Other anticoagulants have significant prospects for use in anti-thrombogenic modification. Hirudin is a 65 amino acid peptide, which is a highly selective direct thrombin inhibitor; it is independent of antithrombin III or cofactors and is not inactivated by platelet factor 4 [12, 13]. There are equivalents such as lepirudin, which was obtained by recombinant technology from a medical leech and used to treat heparin-induced thrombocytopenia, and which is a 65 amino acid polypeptide capable of binding firmly to both the catalytic site and the expanded site for recognition of thrombin substrate [14]. Another similar polypeptide is bivalirudin, a synthetic polypeptide of 20 amino acids that directly inhibits thrombin by a mechanism similar to that of lepirudin [15].

When vascular implants are modified with antiplatelet agents, an increase in thrombotic resistance is also indicated, primarily when used in combination with anticoagulants. The most widely known drug that inhibits platelet activation and aggregation is acetylsalicylic acid (Aspirin). The mechanism of its action consists in suppressing the biosynthesis of thromboxane A2 located in platelets; acetylsalicylic acid is also used as an anti-inflammatory and antipyretic agent [16, 17]. Iloprost is of great interest to researchers as an anti-thrombotic agent for the treatment of vascular prostheses, as it not only inhibits platelet functions, but also prevents vascular spasm, contributing to their expansion, and also protects the endothelium [18, 19].

The listed anticoagulants and antiplatelet agents are used actively in the development of vascular implants such as prostheses, stents, and tissue-engineered grafts. However, there are various approaches to the immobilization of drugs on the surface of products.

Vascular implants with thromboresistant properties. The implantation of any vascular prosthesis or device causes proteins to adhere to its surface, activation of the complement system and platelets, and also causes a foreign body reaction [6]. The nature of the implant interaction with the blood is determined mainly by its type, material properties, blood flow parameters, and the implantation site. Also, in order to improve biocompa-

tibility and thrombotic resistance, the features of the implant material are of great importance when choosing the method of its modification.

Synthetic vascular prostheses. Synthetic blood vessel prostheses based on PTFE and PET have high strength and demonstrate high efficiency in prosthetics of large vessels, for example, in the reconstruction of the aortoiliac segment. However, small-diameter prostheses that are implanted into vessels with slow blood flow and high blood flow resistance in coronary artery bypass grafting, infrainguinal, and other reconstructions have poor patency as a result of early thrombosis and neointimal hyperplasia; this necessitates additional anti-thrombotic modification of the inner surface of synthetic prostheses.

To increase thrombotic resistance of vascular PTFE prostheses, Lin *et al.* covered the inner surface of the implants with heparin using CARMEDA® Bioactive surface technology (W.L. Gore & Associates, Inc. and Berlin Heart GmbH) [20]. This technology consists of preliminary partial depolymerization of non-fractionated heparin by deamination of nitrous acid, resulting in heparin molecules with a reduced molecular weight, which contains an individual chemically reactive aldehyde group. On the surface of the prosthesis, a basal layer is formed, consisting of alternating layers of the anionic polysaccharide dextran sulfate and the cationic polymer polyethyleneimine. The resulting substrate contains functional amino groups used for the covalent binding of heparin through its aldehyde group.

The functioning of the modified prosthesis was evaluated *in vivo* in a bilateral dog femoral artery shunt model. PTFE with heparin was implanted on one side in each animal, and as a control, unmodified PTFE was implanted on the opposite side. The study showed that on the surface of prosthesis containing an anticoagulant, platelet adhesion after 24 hours was 72% lower compared to the control. The patency of the heparin-coated implants was 89% versus 44% in control samples; immobilized heparin contributed to a significant reduction in neointimal hyperplasia [20]. The results were confirmed in a similar long-term experiment with the implantation of the prosthesis for 2 years [21].

In succession, Al Meslmani *et al.* immobilized heparin in combination with collagen on the inner surface of PET (Dacron) prostheses [22]; collagen was used to increase the biocompatibility of the implants. Two types of PET prostheses, woven and knitted, were modified in several stages. First, carboxyl functional groups were applied onto the PET surface; the material was then subjected to aminolysis using ethylenediamine to obtain amino groups. Heparin and collagen were covalently linked to the surface of an amino group containing PET, using glutaric aldehyde; this attachment technology enables us to keep active heparin centers accessible for binding to antithrombin III. Modification with an anticoagulant inhibited platelet adhesion, as well as the formation of a fibrin clot on both the PET (Dacron) tissue prosthesis and the knitted prosthesis. The additional application of collagen on the inner surface of the implants stimulated the adhesion of fibroblasts [22].

Another approach to creating medicinal coatings is the use of biocompatible polymers as a carrier [23]; the possibility of heparinization of a PTFE vascular prosthesis using chitosan was established. In order to bind the polymer to the implant, a photosensitive azide group was introduced into the chitosan molecule; the azide group containing chitosan was applied to the PTFE prosthesis and secured using ultraviolet radiation. Heparin was immobilized on a chitosan coating due to the complexing ability of these substances. The chitosan and heparin complex interfered with the adhesion of platelets and other cells on the inner surface of the prosthesis, demonstrated in an *in vitro* experiment after the implants were in contact with blood. In the modified PTFE prosthesis implanted in the saphenous vein of the dogs, there were no blood clots in the lumen, but an active process of remodeling to the walls of the conduits, especially on the inner surface, involving cells, their proliferation and vascularization of new tissues was registered. This approach was primarily aimed at the gradual degradation of the chitosan and heparin complex and its replacement with the endothelial layer [23].

The level of PTFE prosthesis thrombosis was decreased when modified with iloprost in combination with a tissue plasminogen activator (tPA), which converts plasminogen into a plasmin fibrinolytic enzyme [24]. Iloprost and tPA were secured on the inner surface of the implants using the surfactant tridodecylmethylammonium chloride, which provides non-covalent binding of drugs with a negative charge. The week-long implantation period of the modified prosthesis in the abdominal portion of the rat aorta revealed a significant decrease in the probability of early thrombosis compared with conventional PTFE conduits [24].

Heise *et al.* used a combination of an anticoagulant, PEG-hirudin, and iloprost antiplatelet agent to create an anti-thrombotic coating [25]. The drugs were introduced into a biocompatible, biodegradable polymer solution, polylactide acid (PLA); the vascular PTFE prosthesis was treated twice with the resulting mixture to obtain a dense coating. As a result of the 6-week implantation of the modified

conduits in the femoral artery of pigs, their complete patency was demonstrated, while maintaining the volume of blood flow at the preoperative level and insignificant neointima in the distal anastomosis. This result was achieved due to the PLA's slow degradation and the gradual local release of drugs.

Attention is also drawn to the fact that hirudin serves as an optimal replacement for heparin in the anti-thrombotic modification of implants since heparinized prostheses themselves have several disadvantages. Heparin performs its function by activating antithrombin III, which in turn can inhibit thrombin, but heparin is not effective against thrombin associated with a fibrin clot. Prolonged release of heparin from the prosthesis can provoke the development of thrombocytopenia in some patients and, as a result, can lead to bleeding and thromboembolic complications [25].

The scientific development of coatings with anti-thrombotic agents for modification of synthetic vascular prostheses resulted in several commercial technologies that currently exist on the medical device market, such as BIOLINE Coating (Maquet Cardiovascular, LLC), CARMEDA® Bioactive surface (W.L. Gore & Associates, Inc. and Berlin Heart GmbH), Flowline Biopore® Heparin (Jotec GmbH), PM® Flow Plus Heparin (Perouse Medical) [26].

Tissue-engineered vascular grafts. Tissue-engineered vascular grafts currently represent a promising alternative to synthetic blood vessel prostheses. When developing useful vascular grafts and creating a thromboresistant surface, the complexity of the combinations of various materials used in their manufacture and a structure that mimics the native extracellular matrix should be taken into account. The primary materials for tissue engineering grafts are biocompatible, biodegradable polymers with high strength and optimal stress-related properties such as polycaprolactone (PCL), PLA, polyglycolic acid (PGA) and their copolymers, for example, a poly(lactic acid-*co*-glycolic acid) (PLGA), a poly(L-lactide-co-ε-caprolactone) (PLCL) [5].

The development of vascular grafts generated by electrospinning from PCL bound covalently to heparin molecules was demonstrated by Duan *et al.* [27]. Heparin was attached to PCL using a reaction mixture of N-hydroxysuccinimide (NHS) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) before graft manufacture; this binding of the drug is much more durable and more effective than a simple introduction into the polymer or adsorption on the surface of the finished product. *In vitro* studies have shown the presence of excellent anticoagulant properties in vascular graphs of heparin-bound PCL, as well as a higher biodegradation rate and hydrophilic property compared to PCL alone. The implantation of grafts with heparin in the femoral artery of dogs exhibited the positive effects of these properties on the patency, and regeneration of the vascular wall [27].

A more complex tissue-engineered vascular graft was proposed by Norouzi and Shamloo [28]. The inner implant layer was created using the co-electrospinning of PCL and gelatin to obtain two fiber types. The outer layer was formed by lyophilization of a gelatin hydrogel, which enabled material to be obtained that has large pores for efficient cell infiltration into the graft wall from surrounding tissues. In order to impart anti-thrombotic properties to this structure, heparin was introduced into PCL and gelatin solutions, and then emulsion electrospinning was performed. Due to this approach, the anticoagulant molecules were sealed inside the fibers; their release occurred during the polymer degradation and contributed to a decrease in platelet adhesion on the implant surface [28].

Successful immobilization of heparin through ionic bonds has also been shown on vascular grafts created by co-electrospinning of PCL and chitosan [29]. Accumulating natural biodegradable polymers, such as chitosan, gelatin, or collagen, to synthetic ones (PCL, PLA, PGA, and PLGA), enables the increase of biocompatibility of implants, while maintaining their strength. Relatively strong ionic bonds ensured a stable release of heparin from the surface of the graft polymer fibers into the environment. An *in vitro* hemocompatibility assessment revealed a decrease in platelet adhesion, a prolongation of activated partial thromboplastin time (PTT), and thrombin time (PT) tests, as well as prevention of thrombogenesis *in vivo* after heparin graft modification [29].

To increase the biocompatibility of tissue-engineered PLA grafts, also obtained by electrospinning, Aslani *et al.* applied the human amniotic membrane lysate to the implant surface, since it is rich in structural and functional extracellular matrix proteins, collagen, elastin, laminin, and proteoglycans [30]. Additionally, to ensure thrombotic resistance of the implant, acetylsalicylic acid was introduced into the PLA solution during electrospinning. PCL biodegradation ensured a slow release of the drug from the graft; anti-thrombotic treatment and coating with extracellular matrix elements contributed to the elevated hemocompatibility of the implant, which was confirmed by *in vitro* studies of hemolysis and blood coagulation [30].

Joint immobilization of heparin and other biologically active molecules on the polymer material surface that can regulate the reaction to a foreign body and implant remodeling have shown promising results on the creation of a successful

thromboresistant vascular graft. Gao *et al.* used layer-by-layer self-assembly technology to create a coating of heparin and selenium-modified polyethyleneimine on fibrous PCL grafts [31]. Modified polyethyleneimine was selected as the catalyst for the release of nitric oxide (NO) from endogenous NO-donors, S-nitrosothiols; NO can reduce the inflammatory response and the growth of neointima, as well as stimulate the formation of the endothelium, which serves as a natural thromboresistant lining of blood vessels [31].

In order to accelerate the formation of the endothelial layer in vascular grafts, vascular endothelial growth factor (VEGF) is commonly used, since it can stimulate the migration of endothelial cells. The combination of VEGF with heparin should provide anti-thrombogenic properties to the surface in the early stages of implantation before the formation of a monolayer of endothelial cells. Consequently, in the manufacture of a vascular graft, heparin and VEGF were introduced into the polymer fiber from a mixture of PLPCL, collagen, and elastin using coaxial electrospinning [32]. The wall of the implant obtained consisted of bilayer fibers, the inner layer of which contained bioactive substances. The release of VEGF and heparin during degradation of the outer fiber layer ensured their dosed delivery prevented excessive entry into the blood flow and possible complications as a result of an overdose. These grafts showed excellent patency and the absence of thrombogenesis during implantation in the abdominal aorta of rabbits [32].

Chemoattractants are another bioactive molecule used in conjunction with anti-thrombotic agents. Heparin can be used not only as an anticoagulant but also as a molecule that binds chemoattractant molecules to the implant surface. The effectiveness of this approach was demonstrated by Wang *et al*. [33]. They created a tissue engineering matrix from a mixture of PLA, PLGA, and PLCL using thermally induced phase separation. This method enables the creation of polymer matrices with micro- and nanostructures. Heparin was conjugated on the matrix surface using a mixture of EDC/NHS and a linker, diaminopolyethylene glycol. A solution of stromal cell-derived factor-1 α (SDF-1α) was included in the heparinized matrix; due to the ability of SDF-1α to bind to heparin on the matrix surface, a coating having anti-thrombotic properties and attracting endothelial cells was obtained [33].

In addition to the introduction of anti-thrombotic agents directly into the polymer or their covalent conjugation on the material surface, nanoparticles can also be utilized as delivery vehicles. A recent study presented the development of a composite tissue-engineered graft containing mesoporous silica nanoparticles with high biocompatibility, a large specific surface area, and an ordered pore system [34]. The heparin on the nanoparticle surface was immobilized through an ethylene glycol molecule. Ethylene glycol acts as a linker and also can enhance the anti-thrombotic effect of heparin due to its ability to inhibit protein adhesion. Nanoparticles loaded with ethylene glycol and heparin were introduced into the graft wall inner layer made of PLGA with collagen by electrospinning. The outer graft layer was formed from polyurethane to provide long-term mechanical support. The release of nanoparticles with bioactive substances contributed to an increase in the anticoagulant properties of the graft material and decreased platelet adhesion on its surface. Furthermore, when implanted in the carotid artery of rabbits, the modified grafts showed high patency, and the inner layer was completely biodegraded after 8 weeks, preventing thrombogenesis and stimulating the regeneration of vascular wall tissues [34].

In general, a wide range of manufacturing techniques for tissue-engineered vascular grafts, as well as the materials used and their combinations, allows the creation of implants with various anti-thrombotic modifications. In this case, both anticoagulants and antiplatelet agents, as well as non-thrombogenic materials, for example, elastin and ethylene glycol, can be introduced into the structure [5].

Endovascular stents. The need for anti-thrombotic modification of endovascular stents is associated with a high risk of thrombosis upon contact with blood; this is due to thrombogenicity of the stent itself, the peculiarity of its installation, and damage to the vessel wall at the site of the implant placement [35]. Currently, the primary approach to preventing thrombosis of a vascular stent is the use of polymer coatings loaded with anti-thrombotic agents.

In 1996, Wiktor (Medtronic, Inc) published the results of a study of 5 types of coatings made of biodegradable polymers (PLGA, PCL, polyhydroxybutyrate-valerate, polyorthoester, and polyethylene oxide-polybutylene terephthalate) and 3 types of coatings of non-degradable polymers (PET, polyurethane, and silicone) applied on balloon-expandable coronary stents. The implantation of stents in the coronary arteries of pigs revealed the processes of thrombogenesis, inflammation, and hyperplasia of fibrous tissue in implants with both biodegradable and non-biodegradable coatings [36].

Later Alt *et al.* suggested using PLA with anti-thrombotic drugs administered for application to coronary stents. Palmaz-Schatz stainless steel stents (Johnson & Johnson) were coated with a PLA solution containing PEG-hirudin and iloprost to obtain a 10 μm thick polymer layer and implanted into the coronary arteries of sheep and pigs

[37]. The results of the study in both animal models were similar; the bioactive coating reduced the inflammatory response to a foreign body significantly and contributed to maintaining the lumen and patency of the stented vessel.

Coronary stents coated with acetylsalicylic acid have great potential for clinical use since patients with coronary artery atherosclerosis have endogenous platelet inhibition, which causes their increased susceptibility to agonists released from endothelium inflammation and activation. The electrospinning method was used in order to modify the stainless steel stents, to expand the stents, a balloon with acetylsalicylic acid is employed; PLGA was utilized as the drug storage [38]. The electrospinning of the polymer containing the dissolved antiplatelet agent was conducted directly on the stent surface, obtaining an implant coated with nanofibres with acetylsalicylic acid. The placement of stents in the abdominal aorta of rabbits revealed the ability of the drug coating to inhibit the platelet adhesion effectively and accelerate re-endothelization.

Several studies have shown the possibility of combining anti-thrombotic agents with other drugs and growth factors to reduce inflammation and regulate the healing process of a damaged vessel wall. Choi *et al*. developed a strategy for modifying the surface of coronary stents with heparin, VEGF, and hepatocyte growth factor (HGF), which, like VEGF, can stimulate endothelial cell division [39]. Hyaluronic acid was used to create a simple biocompatible stent coating, which also functioned as heparin storage. Stents made of a cobalt-chromium alloy were coated with hyaluronic acid conjugated with dopamine and loaded with heparin molecules. VEGF and HGF were immobilized on the coating due to the presence of the heparin-binding domain in growth factors. This coating accelerated the formation of a monolayer of endothelial cells [39].

A combination of heparin with VEGF has been applied to the development of stents for the treatment of aneurysms [40]. The metal stent was coated with PLCL nanofibres made by emulsion electrospinning with the incorporation of bioactive molecules. A study of the functioning of a drug-coated implant on a model of subclavian artery aneurysm in rabbits revealed the separation of the aneurismal dome from the blood flow and complete patency of the artery. The release of heparin and VEGF prevented platelet adhesion, thrombosis, and neointimal hyperplasia in a mounted stent [40].

Similar results of implantation in the development of stents for the treatment of aneurysms were explained by Liu *et al*., who used heparin with a lipid-lowering drug rosuvastatin calcium to create an anti-thrombotic coating [41]. Rosuvastatin, a statin that, in addition to lowering blood cholesterol, can inhibit the proliferation of smooth muscle cells in blood vessels and the activation of platelets, stimulate endothelization, and suppress the inflammatory response. The coating, as in the previous study, was made from PLCL nanofibres. However, the nanofibres were obtained by coaxial electrospinning, which resulted in a structure of a drug-containing core with a polymer shell. This method of introducing bioactive substances enables a prolonged release from polymer fibers compared to emulsion electrospinning [41].

The possibility of using heparin with rosuvastatin was uncovered when creating coatings for various types of commercial stents, such as cobalt-chromium (Medtronic Hellas), nitinol Complete SE (Medtronic Hellas), and stainless steel Visi-Pro (Bard PV Hellas) [42]. Stents were coated with two layers of nanofibres obtained by emulsion electrospinning of biodegradable cellulose acetate. The first layer consisted of polymer fibers with rosuvastatin, and the second layer contained heparin. Studies demonstrated a steady release of drugs from the coating within 4 weeks; however, about 50% of the injected drugs were released during the first 8 days [42].

The creation of anti-thrombotic coatings is also relevant for non-metallic stents. A group of Chinese scientists developed a seamless bifurcation tissue endovascular stent based on PET and silk fibroin for the reconstruction of the abdominal aorta [43]. The stent surface was modified with heparin, because, despite its high biocompatibility, silk fibroin, like PET, does not have sufficient thrombotic resistance. Heparin was conjugated using an NHS/EDC reaction mixture after pre-coating the implant with polyethyleneimine. The authors proposed a variant of this stent with a woven base of PET coated with silk fibroin with heparin injected for prolonged delivery of the drug to the implant site [44].

Despite the successful use in clinical practice of endovascular stents, including those with drug coatings, the development of the most effective methods for their anti-thrombotic modification to reduce the risk of possible complications in patients is implemented.

Use in clinical practice. Currently, most of the anti-thrombotic modified medicinal products on the market are manufactured using the CARMEDA® BioActive Surface technology. This technology enables the creation of coatings with non-releasing heparin immobilized on the implant surface [26].

Gore Propaten vascular PTFE prostheses (W.L. Gore & Associates) are heparinized using this technology; they demonstrated patency similar to autologous grafts during short-term follow-up after

femoral-popliteal bypass grafting [45]. An analysis of 5-year implantation by Samson *et al.* showed significantly better patency of heparin-modified PTFE prostheses (85.2%) compared with uncoated PTFE prostheses (53.9%) also with femoral-popliteal bypass surgery [46]. In a recent multicenter retrospective study of the long-term implantation of 1,401 Gore Propaten prostheses, the primary implant patency was 67%, which was superior to the value for PTFE prostheses, which according to various sources does not exceed 35% [47].

CARMEDA® BioActive Surface technology has also been utilized to modify coronary stents with heparin until successful vascular implants with coatings that provide release of antiproliferative drugs are widely available. HEPACOAT (Cordis, Johnson & Johnson Interventional Systems) is an example of a heparinized stent that has shown positive results in reducing platelet adhesion and lowering the risk of early thrombosis in experimental studies [26]. However, in an international multicenter prospective study on 3,098 patients, there were differences in the number of thromboses between heparin-modified and unmodified stents [48].

Conclusion. Numerous studies presented in this review demonstrate a wide range of methods for modifying blood vessel prosthesis, tissue-engineered vascular grafts, and endovascular stents with anti-thrombotic drugs to increase their thrombotic resistance. The main approaches of anti-thrombotic modification include conjugation of drugs on the implant surface and the use of biodegradable polymers, which function as a storage and provide prolonged local delivery of drugs, to create a coating. New technologies are aimed not only at inhibiting the process of thrombogenesis but also at reducing the intensity of inflammation and stimulation of the vascular tissue restoration. The combined use of anti-thrombotic agents with biologically active molecules involved in the regulation of vessel wall regeneration is the primary vector for the development of successful vascular implants.

The authors declare no conflict of interest.

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