# Bio Modivasc® Short Clinical Vascular Manual

# Totally Biological and Biomodified (Bio-ModiVasc®) to turn 100% Cytocompatible Novel Tissue specially made to resist infection and degeneration

**Key Words**: totally biological conduit, Perima™, detoxification, graft, biofilm, endothelium, novel totally non-reactive tissue

**Background**

Totally detoxified glutaraldehyde-treated tissue or heart valves have been clinically used in infective endocarditis, and found to be especially resistant to infection. Likewise, the biomodified (Bio-ModiVasc®) Aortic BioConduit with totally biological tissue, including valve and the ascending aorta made of pericardium (for Bentall procedure) to replace the ascending aorta, has been clinically used for more than 20 years, and found to be equally resistant to infection and reinfection.

The straight pericardial graft (Perima™) bifurcations made from the same material have allowed thoracic, abdominal and peripheral revascularization of infected fields, have yielded similar results with low reinfection rates and durability. This complete clinical manual summarizes those results to date.

**Materials and Methods.**

Most patients had infected synthetic grafts or bifurcations or presented with some sort of infection and presented a high risk of re-infection.

Centers were instructed to give 6 weeks of intravenous (IV) with targeted antibiotics and 6 weeks of full anti-coagulation. This is important for studying subjects since it is a method of treatment. 86 patients have been enrolled in this clinical investigation. Biomodified (Bio-ModiVasc®) tissue Perima™ and Perima™ bifurcation data were analyzed separately. (Most recently 177 patients had been analyzed and the results are described below).

The mean age of patients with a Perima™ and Perima™ bifurcation was 67.2 (51-76) and 62.9 (8-83) years at the time of surgery. The Vascular Conduits, Perima™ or Perima™ bifurcations, have been used on compassionate use basis. Most surgeons have declared that this is the only choice available to save life and avoid amputation.

**Results**

Most patients were discharged, and 3 months after surgery had no evidence of infection. A total of 55 patients were followed-up. The average follow-up for surviving patients with a Perima™ or Perima™ bifurcation was 8.8 (1.1-18.9) and 11.0 (0.5-24.7) months. Within the first 30 post-operative days two deaths were reported, neither of which were device-related. After the 30 day post-operative period, eight non-device related deaths were reported. Other non-device related complications included anastomosis bleeding, sepsis, occlusion, amputation and reasons for re-infection.

**Addendum**

We have studied the accumulative data of all the compassionate patients that the biomodified (Bio-ModiVasc®) graft has been used as best as possible. Unfortunately, some patients came too late, and could not be saved. Now that the device is CE-mark approved, it can be used earlier without a lengthy in hospital approval system. The vascular surgeon should know about the

availability of the this biomodified (Bio-ModiVasc®) graft and if the patient is operated on earlier, before they are septic, definitely as you will see in the following, they will have an even better result.

Below are the summary data for the vascular grafts, all products, all countries, all studies. 177 patients total, 10.7% patient reinfection rate, but only 3.4% reinfection rate for the actual conduits. Primary patency 82% and secondary patency 100%.

| | # | % |
|---|---|---|
| Total | 177 | 100% |
| Mean age | 68.6 | |
| Infection | 19 | 10.7% |
| Graft infection | 6 | 3.4% |
| Graft Bleeding | 4 | 2.3% |
| | | |
| Amputation | 9 | 5.1% |
| Occlusion | 18 | 10.2% |
| Pseudoaneurysm | 5 | 2.8% |
| Aneurysm | 0 | 0.0% |
| **Primary patency** | **82%** | **82%** |
| **Secondary patency** | **100%** | **100%** |

| | | |
|---|---|---|
| Early mortality | 17 | 9.6% |
| Late mortality | 22 | 12.4% |
| Total mortality | 40 | 22.6% |
| | | |
| Explanted (complete) | 6 | 3.4% |
| Partial Explant | 2 | 1.1% |

As you will see by the presentation in Vienna Symposium most patients included in multiple studies were very sick, some of them septic, still the surgeon came to the conclusion that they would rather use biomodified (Bio-ModiVasc®) graft rather than perform a long operation to make a bifurcation out of autogenous veins. Autogenous veins are those belonging to the patient themselves, and would be ideally used to prevent any biological rejection of synthetic grafts. The 3 to 4 hour process is long and dangerous for high risk patients, while synthetic grafts, as later discussed, are prone to infection and calcification.

**Summary of the Vienna Presentation**

(See full report of the publication in the complete clinical manual for vascular surgery). The most striking findings from all the above summaries of each presentation are found in the complete clinical vascular surgery summary, they say that that the biomodified (Bio-ModiVasc®) vascular grafts were implanted in severe infection and that 70 percent of the patients had methicillin resistant bacteria (MRSA); also, some surgeons already confirmed that endothelium is formed on the blood contacting surface of the arteries. Still, although 70 percent of the patients had MRSA infections, they all healed, except some patients that were in an advanced state of sepsis, and they came to surgery too late. The patients that came to surgery too late, already generally had the infection spread to the periphery with the formation of biofilm in which bacteria protect themselves with a thin layer of mucopolysaccharides that prevent antibiotics to penetrate this bacterium. See presentation on biofilm or the structure of vegetation in case of endocarditis in the complete clinical manual. Those patients generally cannot survive any operation. Another interesting finding that practically all the investigators claimed was that the primary patency was 80 percent, and the secondary patency was 100 per- cent. Those kinds of results can be achieved only with autogenous vein surgery (great saphenous vein or femoral vein). Unfortunately, to make a bifurcation out of saphenous veins or femoral veins, it is an extremely tedious operation needing 4 to 6 hours, in addition to implanting the bifurcation in the patient. It can take up to ten hours when dealing with patients that are very sick, and many of them cannot survive the operation. Alluding to the fact that if the results with biomodified (Bio-ModiVasc®) arteries continue to perform as in the last four years, it will be a great solution for using biological

tissue with a biomodified (Bio-ModiVasc®) process to be able to do the surgery earlier and obviously save many lives. This is all due to the endothelium formed inside the arteries, which has many antibiotic-like effects of killing bacteria by producing many chemicals that enhance the killing of bacteria, as well as phagocytosis, which unloads the cells of the endothelium to swallow the bacteria and helps in the healing process. (See in full clinical manual the scientific qualities and chemicals produced by the endothelium.)

All the surgeons who have experience with autogenous saphenous veins stated that the results with the bifurcations are at least as good as with the autogenous veins. The only difference is that to tailor the saphenous vein is tedious, and the surgery lasts ten hours—thus, there are higher levels of morbidity and mortality. With the bio bifurcation, it takes only three to four hours. If we can prove and reproduce these results in a larger study, most surgeons will probably not use the saphenous veins.

**Conclusion**

The Perima™ and Perima™ bifurcations seem to resist infection better than synthetic grafts. The fact that the primary patency is 82% while the secondary patency was found to be 100%, shows that once the patient is discharged from the hospital, in 6 weeks, a monolayer forms on the endothelial layer of the Perima™. This proves that the endothlailization plays a significant role in the patency of the Perima™ and Perima™ bifurcation. The recommended method of treatment - perfect debridement, warm antibiotic rinsing of the surgical field, 6-weeks IV antibiotics and 6-weeks anti-coagulation, and surgery before the patient turns to advanced sepsis - generally gives excellent results. Those totally biomodified (Bio-ModiVasc®) Perima™ and biomodified (Bio-ModiVasc®) Perima™ bifurcations are now the conduit of choice in several European centers. The results of previously conducted studies more than a decade ago, have been confirmed with the identical technology of biomodification.

**Introduction**

Synthetic Grafts. Prosthetic vascular graft infection (PVGI) occurs in 1 – 5% of all grafts[1]. Though relatively rare, PVGI is associated with high mortality (25 – 88%) and complication rates[2]. Graft replacement is usually the only appropriate solution. In urgent cases, synthetic material is readily available for vascular grafts. However, synthetic grafts have high occurrences of re-infection after implantation. They create strong foreign body reactions, and do not promote vascularization of the surrounding tissue. Natural encapsulation of the tissue prevents penetration with blood vessels; blood flow to the infected area is required for the body's innate and acquired defenses against bacteria. Based on a review of 12 publications (404 patients), 9.4% (3.7-20.0% range) of patients experienced re-infection after receiving synthetic grafts for an infection related indication.

***Other Alternatives to Reduce Re-infection***. Post-operative re-infection rates are reduced when homografts are used. Unfortunately, the use of human-based tissue grafts do not produce satisfactory long-term results; homografts have a tendency to degenerate after implantation. Based on a review of 18 publications (1006 patients), despite the low re-infection rates (2.1%) over 15% of allograft patients experienced graft degeneration or dilatation problems after implantation, more than double that of synthetic graft patients. The requirement of an allograft donor also makes these tissue grafts difficult to access in times of emergency.

Autogenous vein grafts are highly compatible tissue for tissue grafts, and have optimum re-infection rates[3], but they require vein harvests from the patient, which increases surgery time, and are not readily available in the required diameter and length. The best option is to use animal tissue that can be shaped into the appropriate diameter and length, is readily available for urgent cases and will promote endothelial growth. Biomodified (Bio-ModiVasc®) conduits are the only all biological xenografts that meet these criteria.

***Biomodified*** (Bio-ModiVasc®) ***Tissue Resists Infection.*** Only totally biological detoxified tissue can be 100% cytocompatible[5]. Thus detoxified tissue that can attract endothelial tissue, and like biomodified (Bio-ModiVasc®) tissue, can be considered a true biomaterial. Figure 3 shows an example of biomodified (Bio-ModiVasc®) tissue compatibility.

Synthetic material, polyester or PTFE, are implantable materials but always causes a foreign body reaction and are therefore mistakenly called a biomaterial. These reactions create a collagen layer around the grafts, preventing capillary revascularization of the mesothelium (Figure 1) and facilitate bacterial growth and vegetative infection, or biofilm. True biomaterials are tissues that cause zero foreign body reactions. In our humble opinion, only Bio-ModiVasc® biomodifications can be called biomaterials, because they cause zero foreign body reaction. Thus, any implant made of synthetic materials that insight encapsulation are not biomaterials. The best proof that we are dealing with biological material that never changes its physical characteristics, is the physical experience with the biomodified (Bio-ModiVasc®) bioconduit used for over 21 years. It never dilated and there are no reports of aneurysmal formation. See Galinanes et al. (12).

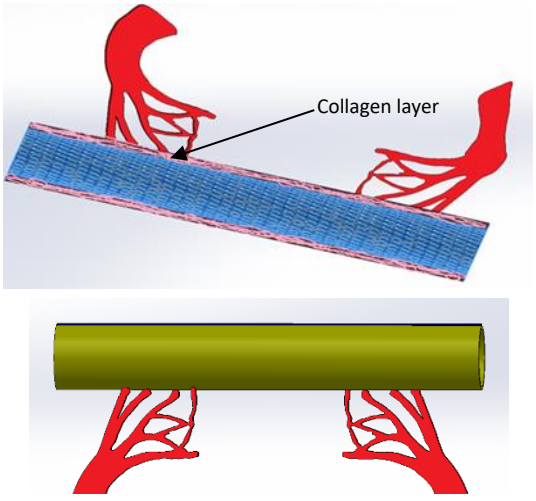

**Figure 1** Biomodified (Bio-ModiVasc®) tissue Treated Graft (green) vs Synthetic Material (blue) and Capillary Revascularization

Biomodified (Bio-ModiVasc®) tissue treated graft does not form a collagen layer around the graft, thus it allows revascularization of the mesothelium to occur. On the contrary synthetic graft material prevents crucial revascularization from occurring. Biomodified (Bio-ModiVasc®) tissue enhances capillary vascularization and thus, helps the Perima™ to eliminate infection. See Figure 3.

Biomodifed tissue on the other hand does not form a collagen layer, allowing capillary revascularization to occur (Figure 1 and 3).

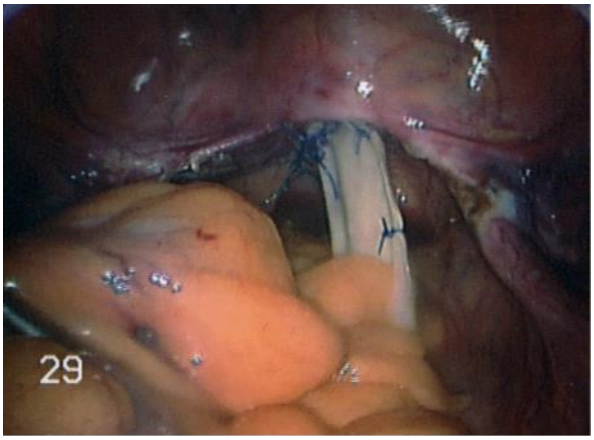


**Figure 2** Another Use of Biomodified (Bio-ModiVasc®) Tissue. A biomodified (Bio-ModiVasc®) tissue patch sutured into a conduit for vault suspension procedure. Image taken immediately after surgery through endoscopy.

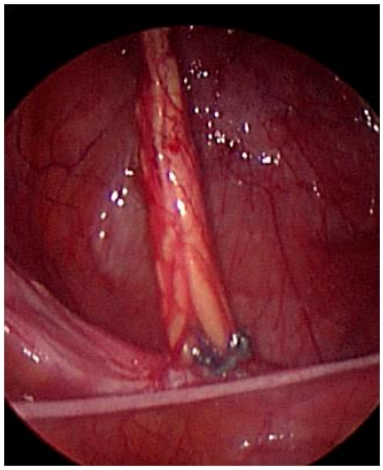

**Figure 3** Another Use of Biomodified (Bio-ModiVasc®) Tissue (at 12 month follow-up). This is a follow-up to Figure 2 also taken through endoscopy. The device was covered by mesothelium as demonstrated through Factor VIII immunoassay. In addition, there is no sign of infection or adhesion and capillaries were able to penetrate the mesothelium.

Biomodified (Bio-ModiVasc®) tissue, a completely biological tissue promotes endothelium and mesothelium growth. The mesothelium metastasizes, enhancing angiogenesis and provides anti-microbial defenses. This layer does not grow on synthetic material or even homografts, as a result, revascularization does not occur, and the graft is prone to infection. In the sternum, where no mesothelium forms and capillaries cannot invade, endothelium formation still resists infection.

***Biofilms***. As a significant complication in cardiovascular surgery, infective endocarditis is often attributed to the development and persistence of biofilms. Adherence of bacterial cells to tissue surfaces is facilitated by the extracellular polymeric substance (EPS) produced by the bacteria. EPS allows microbial cells to adhere to one another and reduces access by antimicrobial agents. Antibiotic-impregnated and silver-impregnated grafts aim to reduce bacterial infection rates, but their limited antimicrobial properties may not penetrate the thick EPS of biofilms and tend to cause severe foreign body reactions. The toxicity of the antimicrobial layer negates any antibacterial properties and may enhance biofilm formation and reduce healing at the wound. Larena-Avellaneda et al. published a wound healing disturbance of 16.7% (72 patients) in patients who received a silver-coated polyester graft for arterial occlusive disease[6]. In addition, the Silzone Heart Valve, containing a sewing ring coated with elemental silver, with the purpose of reducing endocarditis, was recalled from the market due to a high incidence of paravalvular leakage. Tozzi et al. showed that the silver-coated sewing cuff caused a chronic inflammatory response due to the toxic silver[7].

For these reasons, patients with infection must receive full excision of infected synthetic grafts. Biomodified (Bio-ModiVasc®) grafts should only be sutured to native tissue, not partial synthetic grafts.

Bacteria in the blood can be killed with relatively small concentrations of antibiotics but in biofilm, due to the protective layer, the bacterial community creates a muco-polysaccharide layer that prevents antibiotics from penetrating the biofilm. Consequently, a 100 to 1000-fold higher concentration of antibiotics would be necessary[8]. A concentration this high, would be lethal to patients. 900 to 1500 times higher concentration of antibiotics in the blood would be lethal to patients, see extensive discussion and slide presentation (of the biofilm in the complete clinical manual). Thus, endocarditis or abscess are considered surgical disease and not medical, but the combination of surgical and medical treatment will be beneficial to the patient.

***Endothelium***. Any blood contacting surfaces of a synthetic graft will be covered with a collagen layer, but never with endothelium. In fact, endothelium is not formed on any other vascular graft. In small arteries (<6mm), this collagen layer can cause occlusion. If endothelium is present, the graft will generally stay open.

Endothelial cells are crucial because they can phagocytose bacteria[9] and release fibrinolytic factors. These factors have anti-coagulation properties and prevent deposits of platelet aggregation[10]. These platelet aggregates, if formed, allow bacteria to sit and form biofilm.

In general, any infection in a medical device begins with a non-infected thrombus. The endothelium is not just a layer that smoothens the artery, it is an active layer that combats thrombosis and infection. Although most infections are external to the graft, the presence of endothelium eliminates luminal infection.

***The Critical Period***. In here, the critical period is the six week period in which tissue might be prone to infection. During these six weeks, it is very important that each patient receives antibiotic and anticoagulation treatment. If this instruction is followed properly, the re-infection rate would be very low.

***Why do these Graft Prevent Dilatation Without a Synthetic Mesh?*** If the tissue is 100% biocompatible, it will not be perceived as a foreign body, therefore degeneration will not occur and the original strength of the tissue is maintained. Once endothelium forms, the graft becomes part of the body and its physical characteristics are retained permanently. To date, no dilatation has been reported for the BioConduit, even after 22 years.

***BioConduit™.*** The Perima™ is a non-valved modification of the currently CE Marked product, the biomodified (Bio-ModiVasc®) BioConduit™-with the exception of a porcine valve component at its proximal end. While the BioConduit is intended for the ascending aorta, the Non-Valve Conduit, which is Perima™ large diameter (19mm to 27mm) is intended for surgery of the thoracic aorta and abdominal aorta. Smaller Perima™ diameters are intended for peripheral and vascular surgery. Aside from the valve mounting process, the manufacturing process is identical.

Specifically, over 6,500 BioConduits have been implanted over 23 years. There have been no reports of thrombosis and deterioration, and the infection resistance has been demonstrated to be as effective as the “golden standard” homografts[11].

At one year, the BioConduit’s infection rate was 0.16% (1 re-infection out of 667 patients), which is notable given that the device has been used most commonly in patients either presenting as septic or with a local infection requiring reconstruction of the aortic root[12,13,14,15].

Even if antibiotics manage the re-infection, the valve will ultimately calcify. Once damaged, endothelium will be replaced by fibroblasts. As our research shows, a lack of endothelium in a

single valve cusp can host bacteria, promote biofilm and eventually cause life-threatening complications that require immediate surgery.

This success is presented despite the delicate/urgent condition exhibited by patients who receive the device; An average EuroSCORE of 45.0 for the patient cohort has been observed[11,12,13]. Most of the publications of the BioConduit are in patients which are extremely sick, at high risk for re-operation, or present with an infection. The biomodified (Bio-ModiVasc®) product line has been typically utilized by surgeons who cannot readily find a homograft to treat infection, or need to reduce operative times.

One center reported pseudoanuerysm and dissection into the aorta, but the issue was surgical technique and not device related. This center also reported pseudoanerysm rates with homografts of 73%, far above the cardiac surgeon average of <5%[16]. Unlike synthetic material, the treated all-biological tissue does not elicit a foreign body reaction, hence bleeding or oozing must be dealt with immediately using finer monofilament sutures. Aldehyde based glues and polyester sutures are contraindicated.

However, the most recent publication of December 2019 by Blehm et al., in which the authors are comparing the bio conduit (midterm) with the Medtronic stentless freestyle stentless valves. They implanted 202 biomodified (Bio-ModiVasc®) bio conduits with 65 freestyle stentless valves. According to the authors, for both valves, the results are good and in most parameters, there is no statistical significant difference. However, in all parameters, like ease of implementation, length of the extracorporeal times, the possibility to oversize (which gives surgeon to implant one or two sizes bigger to better the hemodynamics), they saw this as a major advantage, and since the freestyle is a relatively short valve, with the bio conduit, they never needed to extend the valve with the synthetic graft which can be problematic when replacing the valve for infection. Moreover, in 36 months approximately 10% of the patients that had the bio conduit were alive compared to the freestyle, see Figure 1 below, published in the previously mentioned article. In our opinion, if the number were larger, this number would be statistically significant. Another interesting point, the fact that they had 202 patients with the bio conduit and only 65 with the freestyle, attests to a preference of the surgeons about which valve they want to use.

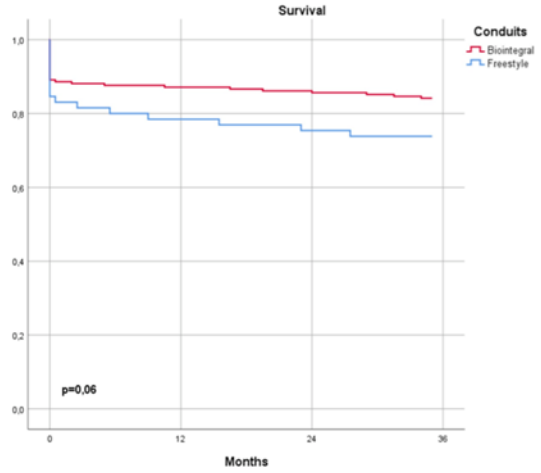


**Figure 4:** see narrative above

***Perima*™**. Prior to this product being on the market, the biomodified (Bio-ModiVasc®) internal mammary artery (IMA) was in use and though results were good, as stated by Avsar et al., "these [biomodified] IMAs offer a good alternative to synthetic grafts and we are of the opinion that these have qualities to warrant their eventually replacing synthetic grafts"[8], pericardium was found to be an even better material. First, pericardium can be suture for any size and diameter while the IMA was limited to the available size. Secondly, the IMA could not be re-adjusted or fixed like pericardium. Finally, when pressurized, pericardium can bend and keep tissue from kinking. This is due to the specific technology of making arteries out of pericardium, becoming more malleable, even better than Dacron or Teflon grafts.

***Presentation by Lachat, M. et al presented in New York and sent to us in personal***

***communication***. In this study, 20 patients received biomodified (Bio-ModiVasc®) conduits for an infectious abdominal aortic aneurysm (AAA) repair. Two patients died within the first 30 post-operative days. The cause of death was multiple organ failure in both cases (the patients were in an advanced septic state).

Mean follow-up was 8 months (1-24 range). One patient received endovascular aneurysm repair for an aorta-duodenal fistula during the sixth week. The same patient died 135 days after graft implantation. No dilation or degenerative problems were observed. Infection was reported in one patient.

***Personal Communication between Lachat, M. and us***. From 30 patients who received a bifurcation, 28 had patent bifurcations 10 years after implantation.

***Bifurcation: Presentation by Neumayer, C. at Medical University Vienna***. The biomodified (Bio-ModiVasc®) bifurcation was compared to the autologous superficial femoral vein (SFV) for graft infection and mycotic aneurysm and was determined to be an "excellent conduit for the management of graft infections and infected aneurysms". Biomodified (Bio-ModiVasc®) grafts were exclusively used for infection (6/6) while SFV's were only used for infection 27% (6/22) of the time. This comparison exhibits two important points. First, the biomodified (Bio-ModiVasc®) graft is at least comparable in performance to autologous veins. Two amputations occurred and they were both in SFV's. Follow-up was longer for SFV's - median of 38 months (1-14 years) - compared to the biomodified (Bio-ModiVasc®) graft's median follow-up of 8 months (max 18 months). Nevertheless, 30 day mortality and overall mortality was 16.7% (1/6) in biomodified (Bio-ModiVasc®) grafts. In SFV's 30 day mortality and overall mortality were 9% (2/22) and 27% (6/22) respectively. The second important conclusion is that surgery time while using autologous tissue is extensive (6-8 hours) and facilitates more possible complications and costs. Using an off-the-shelf product minimizes surgery time and costs. Most importantly, it will increase survival rates by reducing the number of patients who come to surgery too late (severe sepsis).

***Summary***. More than 40 years of research were dedicated to developing a processed biological tissue product with the capacity to act like an autogenous vein and have the added advantage of promoting endothelium growth. A good resistance to infection must be equivalent to native graft infection rates. The BioConduit and tissues are processed similarly, and over 21 Perima™ years of clinical experience with the BioConduit shows minimal rates of re-infection. Bovine pericardium tissue used for these products are naturally larger in size; they require fewer anastomoses during production, which reduces potential problems. The Perima™ and Perima™ bifurcation products have similar re-infection rates as native tissue, promote endothelium growth and are readily available without harvesting. Such a product is a priority to patient health and should re-enter the market immediately.

***Methods***

Data collected under the compassionate use program for straight (Figure 5) and bifurcated (Figure 7) biomodified (Bio-ModiVasc®) grafts was analyzed using Excel. Unknowns were not included in the analysis. A compassionate use form was filled out for one patient but a saphenous vein was available and the device was opened but not implanted.

Patients for whom data could not be confirmed or experienced a technical related complication peri-operatively were excluded from analysis. In a study performed in the Netherlands, 55 cases have been also excluded and we are now investigating the reason.

Figures 8 and 9 show successful implantations of the straight graft and bifurcation respectively.

**Figure 5:** Perima™ Straight Graft. The straight conduit is a smaller diameter and longer than we see in the bifurcation (below). The conduit illustrated is inflated with pressurized saline.

**Figure 6**: Perima™ Resisting Kinking. As we can see, under pressure, the Perima™ can curve very nicely without kinking and 6mm diameter Perima™ have been used for dialysis shunt. Several surgeons have found this curvature to be very convenient and easy to puncture.

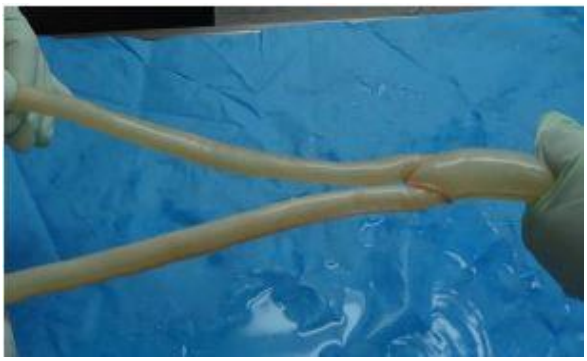

**Figure 7**: A Perima™ bifurcation . Aortic inflow with larger diameter and length of 10 cm and the bifurcation with smaller diameter and length of 25 cm. The length of the bifurcation ranges from minimum 25cm to maximum 40cm. The bifurcated conduit illustrated is inflated with pressurized saline.

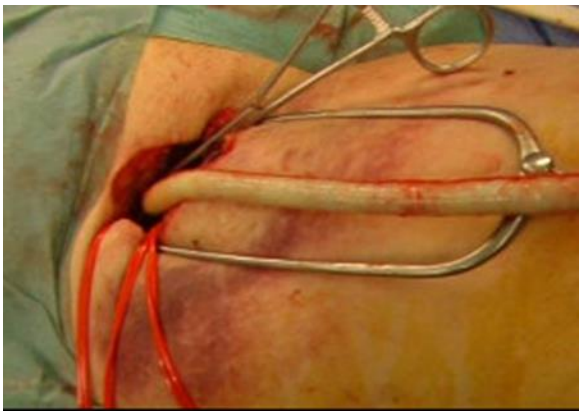

**Figure 8**: Implantation of Longer Artery. The image shows a biomodified artery used for femoral-popliteal bypass. The surgeon sutured the proximal anastomosis first and then would tunnel the artery.

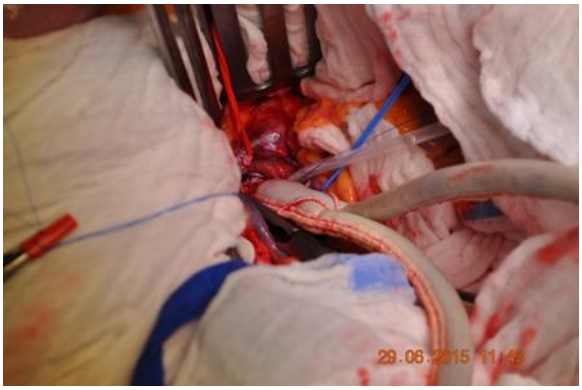

**Figure 9:** Bifurcation Implanted. After suturing the proximal anastomosis, a distal clamp was placed and the clamp at the aorta was removed. The bifurcation can be seen inflated like a normal artery.

## Results

***Patients***. In total, 86 patients received 93 biomodified (Bio-ModiVasc®) grafts (28 straight, 63 bifurcated and 2 unknown) and were enrolled in the compassionate use program. Five patients received 2 biomodified (Bio-ModiVasc®) grafts and one patient received 3 biomodified (Bio-ModiVasc®) grafts. The average age of patients receiving a straight graft was 65.6 years with a range of 22-81 years. The main indication for the use of biomodified (Bio-ModiVasc®) straight grafts was infection in 80% (16/20) of patients. If patients did not receive a biomodified (Bio-ModiVasc®) straight graft, the main risk was amputation in 50% (8/16) of patients.

The mean age of patients receiving a bifurcation was 62.5 years (ranging from 8 to 83 years old). The main indication for use was also infection in 83% (45/54) patients. The primary risk of not using the biomodified (Bio-ModiVasc®) bifurcation was death in 47% (20/43) of patients. Table 1 summarizes characteristics of all patients currently enrolled in .

**Table 1 Patient Data**

| | **Straight graft** | **Bifurcation** |
|---|---|---|
| **Patients** | 23 | 61 |
| **Grafts implanted** | 26 | 63 |
| **Average age** (years) | 65.6 (22-81) | 62.5 (8-83) |
| **Mean Follow-up** (months) | 8.8 (1.1-18.9) | 11.0 (0.5-24.7) |
| **Main indication** (%) | 16/20 (80%) Infection | 45/54 (83%) Infection |
| **Main risks**(%) | 8/16 (50%) Amputation | 20/43 (47%) Death |

*Follow-up.* A total of 55 patients with a total of 61 grafts were followed-up. Twelve patients received a straight graft and 43 received a bifurcation. The average ages of straight graft and bifurcation recipients were 67.2 (51-76) and 62.9 (8-83) years at the time of surgery.

*Early (<30 days) mortality*. Two non-device related deaths were reported within the first 30 days post-operatively. Both patients received a bifurcation and succumbed to sepsis.

*Late (>30 days) mortality*. During a longer-term follow-up period, a total of 9 deaths occurred. None of the deaths were reported to be device related. Sepsis or multiple organ failure were the cause of death in 67% (n=6) of patients while bleeding at the native tissue anastomosis and unknown causes were responsible for one and two deaths respectively.

***Complications***. No device-related complications were reported. The major events were 3 amputations resulting from septic shock in a patient with peripheral arterial occlusive disease (PAOD), poor runoff and heavy peripheral arterial occlusive disease in the second patient and hemorrhage and poor immunological condition in the third patient.. A perforation bleeding event occurred in a patient with two grafts who has undergone bypass of the right led three times. The grafts were reported to be infected and were explanted. Two occlusive events resulted in one thromboctemy and one graft being explanted. The explanted graft was initially implanted in a 65 year old patient with critical leg ischemia (poor runoff), necrosis and infection of soft tissue. Infection was reported in 4 patients. Three of those infections occurred in patients with anastomosis bleeding. The fourth re-infection occurred in a patient with an infected and ruptured PTFE graft.

Of the surviving patients who received a bifurcation, four patients were reported to have a bleeding event. The bifurcation was explanted and replaced with another Perima™ bifurcation in a patient with an abdominal abscess as a result of bleeding from the left inguinal fistula. In another patient the anastomosis bleeding was occurred. A graft thrombectomy on the 27th day post-operatively was necessary for a patient who initially received the Perima™ to replace a silver graft that was preventing healing. Other non-device related complications included sepsis, dehiscence of abdominal wound post-hernia and an infected femoro-femorol bypass. Finally, one patient had septic shock, reperfusion syndrome, kidney damage and an epileptic episode. The patient's condition has improved and is currently recovering while the graft remains patent.

***Infection***. In total, 6 surviving patients, 4 with a straight graft and 2 with a bifurcation, have been reported to have an infected Perima™ graft. None were reported to be device related. Interestingly enough, 5 of the infections occurred in patients with bleeding.

**Table 2 Morbidity and Mortality Summary**

| | Straight graft (n=11) | Bifurcation (n=44) |
|---|---|---|
| **Early mortality (%)** | 0 | 2 (4.5%) |
| **Sepsis/MOF** | 0 | 2 (4.5%) |
| **Late mortality (%)** | 0 | 9 (20.5%) |
| **Sepsis/MOF** | 0 | 6 (13.6%) |
| **Native tissue bleeding** | 0 | 1 (2.3%) |
| **Unknown** | 0 | 2 (4.5%) |
| **Survivor Complications** | (n=11) | (n=35) |
| **Amputation** | 3 (27.3%) | 0 |
| **Occlusion** | 2 (18.2%) | 1 (2.9%) |
| **Bleeding** | 1 (9.1%) | 4 (11.4%) |
| **Infection** | 4 (36.4%) | 2 (5.7%) |
| **Sepsis/septic shock** | 0 | 2 (5.7%) |
| **Wound dehiscence** | 0 | 1 (2.9%) |

## Discussion

PVGI, though relatively rare, is associated with high mortality and morbidity. Graft excision, though usually postponed to conservative treatment, is an appropriate solution for infection. The best option for replacement is an autogenous vein as it is the most effective against infection[18]. However, in many cases none are available or suitable. Furthermore, because using autogenous veins requires longer operative times, such a procedure would not be appropriate for high risk patients[19].

Other alternatives are synthetic grafts and homografts. Unfortunately, synthetic material is prone to infection and homografts are limited. Cryopreserved allografts specifically have demonstrated significant degeneration and dilatation problems. Kieffer et al. reported 7 (3.9%) graft rupture related deaths[20] while Pirrelli et al. reported even more concerning results; an overall graft related complication rate of 65% (15/23), including 18 graft ruptures in 12 patients and a 22% (5/23) graft related mortality[21]. Especially when treating patients with infection or at risk of infection when no autologous veins are available, the Perima™ vascular conduit is an excellent option. Along with the BioConduit and the previously CE marked Perima, it has proven anti-infective properties and long-term durability in the toughest cases.

One important consideration is that current practice to treat infection remains relatively conservative and surgery is postponed usually until the patients develop sepsis and require an emergency graft replacement. Early full graft excision following infection would reduce the incidence of sepsis thus also minimizing the rate of complications.

Though overall results were good, considering that most patients came to surgery too late, there is reason to believe that the efficacy of the Perima™ has been underrated by the data presented. First, it has not been confirmed whether the instructions for use were followed accordingly. In order to prevent re-infection, a complete debridement of the surgical area must be performed using warm (45°C) saline and antibiotics. In addition, the patient must receive targeted IV antibiotic and anticoagulation treatment for a minimum of six weeks post-operatively. If the patient is released prior to the six weeks, a 2 week IV antibiotic regime must be followed by 4 weeks of oral antibiotics. Failure to do so jeopardizes the device's ability to promote endothelial growth, angiogenesis and actively prevent infection and thrombosis. Secondly, as previously mentioned and to emphasize its importance, surgery is usually left too late and even though the re-infection rates are low, complication rates associated with sepsis and septic shock would be inevitably high.

***Four reasons why re-infection occurs.*** Six re-infections occurred in surviving patients, but none are device related. The cause of the infection is likely one of the following, (1) anastomosis bleeding, (2) inadequate debridement, (3) urine or bowel fistula and, (4) inadequate antibiotic and anticoagulation treatment.

Since biomodified (Bio-ModiVasc®) tissue does not invite a foreign body reaction, any oozing from anastomosis – contrary to anastomosis done with synthetic material – cannot be stopped relatively fast, thus oozing or bleeding must be terminated and dried completely during surgery. Such oozing can easily turn into a hematoma or a pseudoaneurysm and since the field is still infected, it can become an abscess. This abscess will slowly re-infect the tissue. In other words, oozing is very detrimental to the patient and the graft. Oozing should be stopped using fine praline sutures and proper wound drainage. To prevent oozing, the suture bites should be very close to each other – no more than 1 mm is necessary. Again, using any bio-glue that contains aldehydes is contraindicated since it will re-toxify the biomodified (Bio-ModiVasc®) tissue.

Before implanting the biomodified(Bio-ModiVasc®) graft, bacterial load should be reduced as much as possible. This can be accomplished with thorough debridement and rinsing with warm saline and antibiotics. As the saying goes, "the solution to pollution is dilution". By diluting with warm solution, bacteria become more susceptible to antibiotics and future re-infection is less likely to occur.

To prevent a fistula, especially in the aortic anastomosis – less delicate than distal anastomosis – it is worthwhile to cover it with a biomodified (Bio-ModiVasc®) patch to separate between the viscous and the anastomosis. An even better alternative, since the bifurcation is retroperitorial cavity the company recommends to approximates the edges and suture them (close the peritorium) to separate the retroperitorial cavity space form the bowel. If the peritorial layer is infected or cannot be approximated, the company strongly recommends to cover the gap with a biomodified (Bio-ModiVasc®) patch. It is important on both sides of suturing the patch to the peratorium to leave a 2 cm gap between each suture, allowing the peritorial cavity to heal and empty all seroma to the abdominal cavity (drain it).

Finally, as mentioned early on, target intravenous antibiotics and anticoagulation for 6 weeks postoperatively will help maximize graft efficiency.

Given the life and limb threatening conditions of the patients receiving biomodified (Bio-ModiVasc®) grafts, it is evident that as a substitute for autologous tissue, the Perima™ is best option. The results of the compassionate use program show that the vascular conduit and biomodified (Bio-ModiVasc®) CE marked Perima™ conduit are identical in performance. Based in the clinical results of the BioConduit and all the clinical studies we have done, the company has now received CE certification. Now that the CE mark certificate has been granted, the clinical results will be even better. More data is currently being collected to further assess the performance of the device.

**Conclusion**

The results of our compassionate use study indicate that the Perima™ vascular conduit matches the performance of the previously CE marked Perima™.Nonetheless, it is crucial that recommendations for use are followed correctly: (1) oozing must be stopped and dried completely, (2)complete debridement and rinsing with warm saline and antibiotics must be performed, (3) the aortic anastomosis can be covered with a biomodified patch to prevent a fistula and, (4) targeted intravenous antibiotics and anticoagulation should be given to each patient during the critical 6 week period following the surgery.

As validated by multiple users of the product, the study presented and the pressure from surgeons who are very satisfied with the product, the biomodified (Bio-ModiVasc®) Perima™ and Perima™ Bifurcation are excellent options to manage graft infection and save the lives and limbs of patients who present with an infection. Moreover, since many patients are presented to the vascular surgeon with sepsis, the knowledge that a good alternative

exist will urge the treating physicians to refer patients to surgery earlier. Thus even better results are expected. In addition, all the patients older than 65 or are at higher risk for infection can now have the Perima™ or the Perima™ bifurcation implanted in case of severe stenosis or occlusion.

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**Appendix A**

Received: 7 May 2018 | Revised: 3 January 2019 | Accepted: 7 January 2019

DOI: 10.1111/xen.12496

BRIEF COMMUNICATION

WILEY Xenotransplantation

# Replacement of infected aortoiliac vascular grafts with bifurcated BioIntegral Surgical No-React® bovine pericardial xenografts

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**Abstract**

The infection of a vascular prosthesis is potentially fatal, and its effective treatment still remains the greatest challenge for vascular surgeons. We present our initial experience using bovine pericardial vascular prostheses to replace infected aortoiliac vascular grafts. Six consecutive patients with infection of the graft were prospectively included in this study. Infection of the vascular graft was confirmed by clinical symptoms, laboratory tests and the results of computed tomography and positron emission tomography/computed tomography. In all cases, the infected aortoiliac graft was surgically removed and replaced by the bovine—pericardial BioIntegral aortic-bifemoral prosthesis. Technical success was achieved in every case with no in-hospital or 30 days mortality. One patient required revision of distal anastomosis due to recurrent bleeding at day four after surgery. One patient presented with upper gastrointestinal tract bleeding during the postoperative period, which was managed endoscopically. The mean hospital stay was 14 days (range 9-19). The control CT scan performed 2 months after surgery showed significant regression of abscesses and periprosthetic inflammation. Two patients died within 32 months of follow-up: one due to heart attack, the other due to generalized sepsis, which was correlated with the previous infection. Four patients are still in follow-up. The BioIntegral prosthesis is patent in all four cases, with no clinical or ultrasonographic signs of infection. Our brief investigation shows that a bovine pericardial prosthesis may be a valuable option in the treatment of vascular grafts infections.

## 1 | INTRODUCTION

Vascular graft infection is a rare but serious complication in vascular surgery. It may lead to the amputation of a limb or possibly the death of a patient. According to the literature, the incidence of infections after vascular surgery ranges from one to six percent and are highly dependent on the location of the prosthesis.[1] Infections of aortofemoral prosthetic grafts are associated with a mortality risk as high as 33%-58%, whereas below the inguinal ligament the mortality risk is approximately 22%, with a risk of limb amputation of 79%. The introduction of endovascular techniques in the treatment of both aortic aneurysms and chronic lower limb ischemia significantly reduced infections by limiting direct contact with the implanted material, minimizing surgical trauma, and shortening the duration of the

**Appendix B**



**Mid-term single-centre outcomes of BioIntegral compared to Freestyle aortic conduit implantation**

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**ABSTRACT**

BACKGROUND: Full aortic root replacement with biological conduit has limited options. This non-randomized cohort study aims to compare mid-term clinical and hemodynamic results of the BioIntegral (BI) composite biological versus the stentless Freestyle (FS) conduits in patients undergoing full aortic root replacement.

METHODS: From February 2013 to July 2017, 265 patients underwent aortic root replacement at a single institution (BI n=202, FS n=65). Preoperative, intraoperative and postoperative parameters, complications including stroke, myocardial infarction (MI), endocarditis and reoperation were studied. Hemodynamic performance of both conduits was analysed by echocardiography. Target endpoints were 30-day mortality, 2-year survival, 2-year freedom from major adverse valve-related and cardiovascular events.

RESULTS: Wider BI conduits were used (BI 27±2mm vs FS 25±2mm, p<0.0001). The BI group had shorter cardiopulmonary bypass (BI 165±67min vs FS 200±78min, p<0.0001) and cross-clamp (BI 102±36min vs FS 122±40min, p=0.001) times. Thirty-day mortality was similar in both groups. There were fewer conduit-related reoperations in the BI group (BI 0% vs FS 3%, p=0.012) but higher postoperative atrial fibrillation (BI 31% vs FS 17%, p=0.025). No significant differences were observed for stroke (BI 5% vs FS 10%, p=0.947), MI (BI 3% vs FS 4%, p=0.583), or infective endocarditis (BI 0% vs FS 2%, p=0.077). No significant hemodynamic differences were evident on follow-up echocardiography while an improved overall survival trend was seen in the BI group (p=0.062).

CONCLUSIONS: FS and BI provide comparable clinical midterm results and hemodynamic parameters. Simplified implantation technique providing shorter cardiopulmonary bypass and operation times are advantageous for BI.

KEY WORDS: Root replacement; BioIntegral conduit; Biological full root conduit