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Confirmation of Safety, Performance, and Usability of Sternotomy Suture Materials in Patients Undergoing Sternotomy with Early Functional Follow-Up Treatment

Attainment of the Academic Degree Doctor of Medicine
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Notes

The entry of the Evaluator and date of the Viva Voce Exam (Defense) follows the provision of the papers by the Medical Faculty Carl Gustav Carus of the Technical University of Dresden. After the Defense, the above-mentioned record of the postgraduate degree of which five compulsory copies are in handwritten or printed form, should be submitted to the relevant Medical Library.

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1. Background

Median sternotomy, first popularized by Julian et al. in 1957, has become the most commonly used incision in cardiothoracic surgery. Although the closure of this incision is usually simple and straightforward, healing complications such as instability, nonunion, and infection occur in 0.3% - 8% Patients undergoing cardiac surgery (Alhalawani & Towler, 2013). These complications increase mortality and prolong morbidity (Malhotra et al., 2014).

Despite several technical variations and improvements in sternal closure over the years, a small percentage of patients experience sternal wound complications, among which deep infections involving the sternal bone and mediastinum are the most relevant (Rupprecht & Schmid, 2013).

Although many factors are known to increase the risk of sternal wound infection (SWI), some studies have reported that nickel is a risk factor for SWI. Sternum closure using steel wires containing nickel is a potential risk factor due to the known allergic reactions to this material (Lopez et al., 2016; Teo & Schalock, 2016) and the number of patients with an "undiscovered" allergy is underreported.

Stainless steel wires have been extensively used for decades and are well established as surgical suture materials. Titanium wires have only been used as an alternative to steel wires in patients with known allergy to nickel. However, there is a paucity of literature regarding the safety of using titanium wires compared to that on the safety of steel wires for sternum closure after cardiac surgery in terms of early sternal dehiscence, sternal infection and wound pain. Therefore, this study aimed to demonstrate the non-inferiority of titanium wires, even in patients without a known allergy. In addition, the handling of titanium wires compared to that of steel wires was documented by surgeons.

1.1. Anatomy of the sternum

The sternum is a flat anteriorly convex bone. It is connected to the first seven pairs of thoracic ribs through the costal cartilage. The normal length of the sternum is 15–20 cm. The sternum consists of three main parts (fig. 1): the manubrium, corpus (body), and xiphoid. The manubrium is the densest region of the sternum. The corpus is fused directly below the manubrium; it connects the seven intercostal ribs with the sternum and is longer but narrower, than the manubrium. The xiphoid process is fused below the corpus and is not connected to any of the thoracic ribs. The sternum consists of compact (cortical) and cancellous (spongy) bones. It has a higher percentage of cancellous bone than that of the

compact bone because it encloses the lungs and must be capable of some flexibility during respiration (Alhalawani & Towler, 2013).

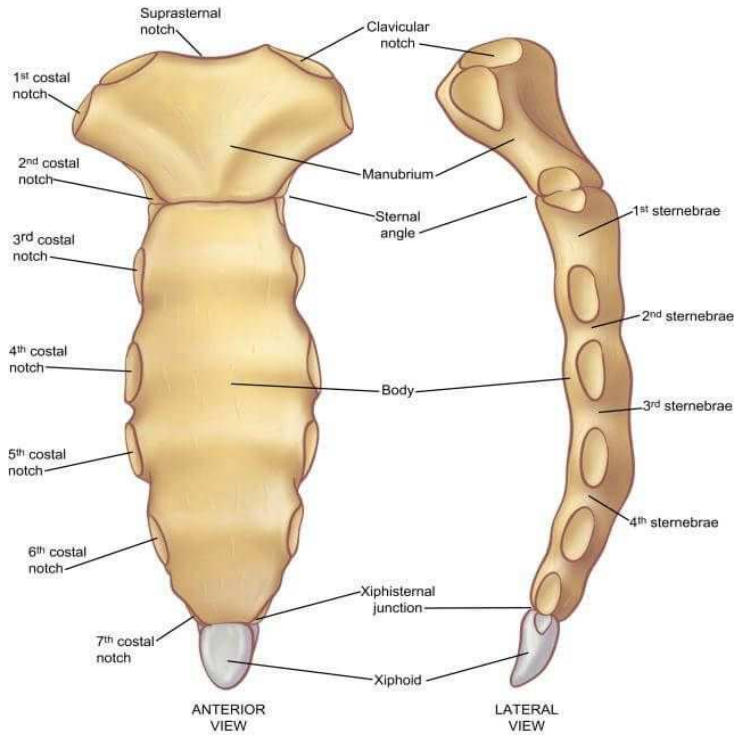

Figure 1 Anatomy of the sternum (anterior and lateral views of the sternum) (Image Source: Copyright free image)

1.2. Blood supply of the sternum

The blood supply to the sternum is mainly derived from the medial horizontal branches of the right and left internal thoracic arteries, which originate directly from the first part of the subclavian arteries bilaterally or occasionally from a common trunk. The internal thoracic artery gives rise to sternal, anterior intercostal, perforating, and noncollateral branches. The sternal branches of the internal thoracic arteries, which are the main branches supplying the sternum, are primarily located in the intercostal spaces. Both the sternal and perforating branches appear to contribute to the sternal blood supply. The blood supply to the sternum plays a major role in the healing process after sternotomy procedures. Further, it is important to understand the blood supply of the sternum as sternal infections are not uncommon after internal thoracic artery harvesting for coronary artery bypass grafting. For venous drainage, the internal thoracic veins drain into the brachiocephalic vein on each side (Berdajs et al., 2006; Gupta et al., 2002).

1.3. Basis and phases of acute wound healing

There are four phases of wound healing:

- Hemostasis establishes the fibrin provisional wound matrix, and platelets provide the initial release of cytokines and growth factors in the wound.
- Inflammation is mediated by neutrophils and macrophages, which remove bacteria and denatured matrix components that retard healing and are the second source of growth factors and cytokines. Prolonged, elevated inflammation retards healing due to excessive levels of proteases and reactive oxygen species that destroy essential factors.
- Proliferation: fibroblasts, supported by new capillaries, proliferate and synthesize disorganized extracellular matrix (ECM). Basal epithelial cells proliferate and migrate over granulation tissue to close the wound surface.
- Remodeling: fibroblast and capillary density decreases, and the initial scar tissue is removed and replaced by ECM, which is more similar to the normal skin. ECM remodeling is the result of balanced, and regulated protease activity.

Cellular functions during different phases of wound healing are regulated by key cytokines, chemokines, and growth factors. Cell actions are also influenced by interactions with ECM components through integrin receptors and adhesion molecules. Matrix metalloproteinases produced by epidermal cells, fibroblasts, and vascular endothelial cells assist in cell migrations, while proteolytic enzymes produced by neutrophils and macrophages remove denatured ECM components and assist in initial scar tissue remodeling (Fitridge & Thompson, 2011).

1.4. Biomechanics of the sternum

Three-dimensional multiple forces (cyclic tension) are imposed on the sternum during respiration cycles because of the muscle forces in different directions. The forces acting on the sternum can be tested using biomechanical analysis. Generally, both static and dynamic means are used for testing sternal closure techniques; static testing to measure the force at which the fixation technique fails owing to a steadily increasing load and dynamic testing to mimic the forces applied on the sternum during events such as breathing and coughing (Alhalawani & Towler, 2013). Most studies have analyzed the biomechanics of the sternum from three loading perspectives: transverse shear, lateral distraction, and longitudinal shear.

Casha et al. (1999) reported that for a closure technique should be able to resist twice the maximum potential stresses applied on the sternum to provide suitable stability (Casha, Yang, Cooper, et al., 1999). Alhalawani et al. reported that indirect measurements resulted in a force of 260N imposed on the sternum during a 5.6 kPa pressure-generating cough. They also demonstrated that the distending pressure of a normal cough was 13.3 kPa, imposing a force of 56 kg (555.3 N= Newtons) on the sternum, whereas the distending pressure of a maximal cough reached 39.9 kPa, imposing a force of 168 kg (1666 N) (Alhalawani & Towler, 2013).

Many biomechanical studies using various models have demonstrated the stability of wiring techniques. Casha investigated six different sternal wiring techniques using an equivalent device, stainless steel wire from Ethicon, UK, USP 5. For the six wiring techniques, the maximum force applied was 20 kg because the used device untwists at the range of 20–22 kg. Accordingly, displacement was measured at the starting point of material deformation. The Laplace law was used to measure the maximum coughing force on the sternum after median sternotomy, and the results indicated that all wires might untwist under severe coughing forces (range, 150-168 kg) (Casha, Yang, Cooper, et al., 1999). Thus, Casha reported that a closure device should have a safety margin that can withstand double the maximum force applied. Another study has also recommended the use of at least eight straight wires four figure-of-eight wires or four multi-twist wires (Alhalawani & Towler, 2013).

1.5. Post-sternotomy complications

Major sternal complications, such as dehiscence, mediastinitis, osteomyelitis, sternal wound infection (SWI), and/or non-union/displacement are infrequent after cardiac surgery. However, such complications, result in considerable morbidity, mortality, and resource utilization (Fedak et al., 2010).

1.5.1. Dehiscence and sternal instability

Sternal dehiscence is directly related to SWI and occurs due to sternal fracture, osteoporosis, coughing, obstructive pulmonary disease, and other force-imposing activities. It is the cause of up to 40% mortality and morbidity after median sternotomy, with an incidence rate of 0.3%–8% (Alhalawani & Towler, 2013). Noninfected sternal instability (SI) has also been reported. An inadequate mobilization of the patient with high traction forces to the sternal edges resulting from severe coughing can tear the wires through the sternal bone (fig. 2). This rapid process destroys osseous integrity and leads to immediate SI. A more gradual course creates a gliding trauma that leads to

cartilaginous metaplasia with less movement of the fragments, but it usually ensues chronic pain syndromes (Rupprecht & Schmid, 2013). SI occurs as a result of sternum separation at the midline, causing abnormal and/or excessive micromotion due to fracture or disruption of sternal wires. Deep wound breakdown (dehiscence) and secondary instability of sternal closure facilitate tissue infection and mediastinitis (Robicsek et al., 2000).

Pain and sternal clicking are two of the most common complaints reported by patients with SI (Chepla et al., 2011). Thorough history and physical examination are used to diagnose SI, which is then confirmed with subsequent radiographic and ultrasound imaging studies (Chepla et al., 2011; El-Ansary et al., 2007). SI is divided into (1) sternal dehiscence if diagnosed within 2 weeks postoperatively and (2) sternal nonunion if it persists for > 6 weeks postoperatively. SI can be classified as complete (separation may involve the entire sternum) or partial (separation may usually involve the lower third of the sternum) (El-Ansary et al., 2000; Robicsek et al., 2000). The lower third of the sternum has less blood supply and is subject to more distractive forces resulting from the “bucket-handle” motion that increases the lateral diameter of the lower ribcage during respiration (El-Ansary et al., 2000). The occurrence of postoperative SIs and associated complications is associated with enormous physical and psychological stress for the patient and an increased mortality rate. Furthermore, it is very costly due to additional costs incurred owing to the longer length of hospital and treatment of complications, including intensive therapy, radiological and microbiological examinations, and complex surgical interventions. The average cost of surgical intervention approximately € 36,000. In addition, the costs of follow-up treatments outside the hospital cannot be precisely quantified (Loladze et al., 2017).

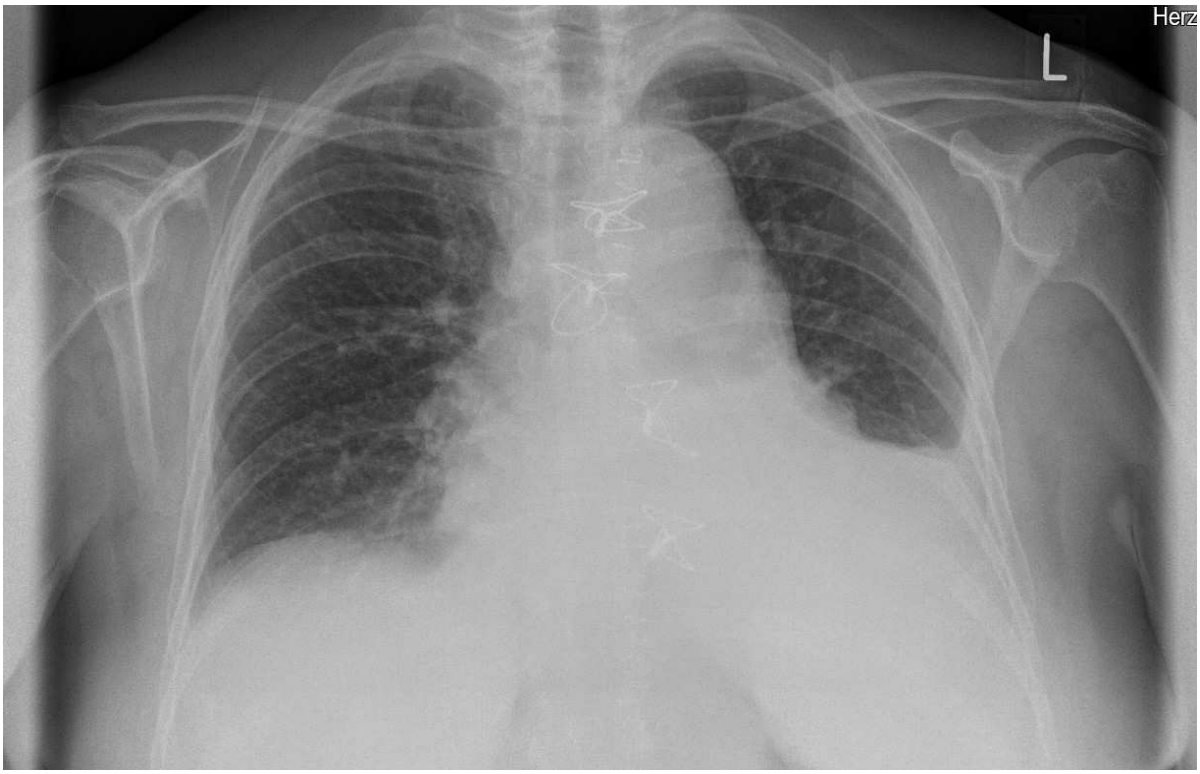

Figure 2 Chest X-ray AP view showing migration of sternal wires due to postoperative sternal instability. (Image Source: Wound clinic, Heart Centre Dresden)

1.5.2. Mediastinitis and deep SWI

Deep SWI with sternal instability is the most deleterious situation. A maintained structure of the sternal halves is less frequent and is mostly related to a loosening or rupture of sternal wires. The ongoing movement of sternal edges promotes inflammation, effusion, and secondary infections. Deep SWI and SI are frequently associated with extensive bone loss, while total destruction of the sternum only occurs when the wires cut the bone into small pieces. Most patients suffer not only from extensive sternal infection but also from severe respiratory problems, often associated with pneumonia (Rupprecht & Schmid, 2013).

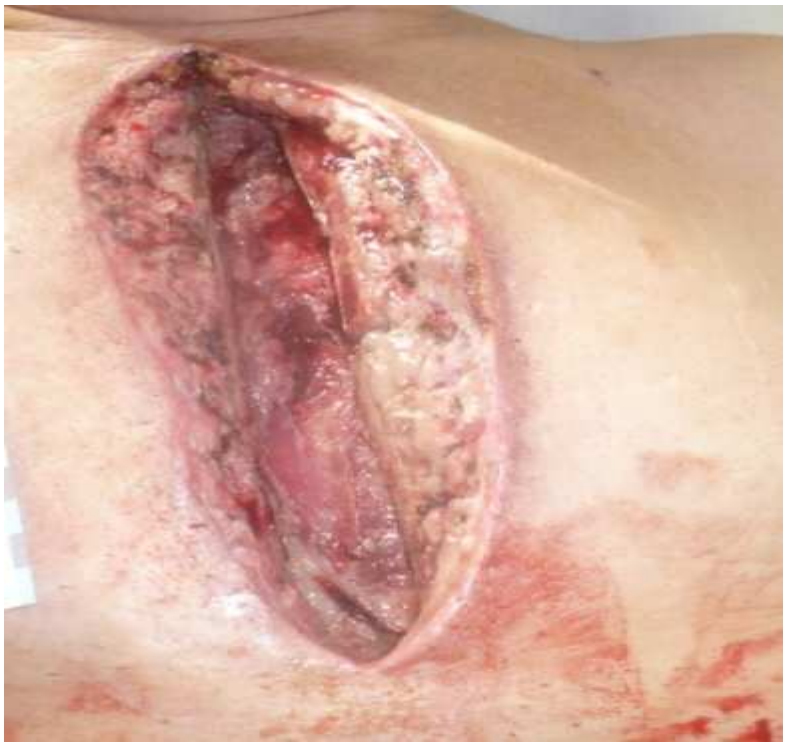

Figure 3 Post coronary artery bypass grafting wound infection and mediastinitis. (Image Source: Wound clinic, Heart Centre Dresden)

According to the Centers for Disease Control and Prevention (CDC) guidelines, mediastinitis is diagnosed based on at least one of the following criteria:

- The culture of mediastinal tissue or fluid shows positive findings.
- Gross anatomical or histopathological examination reveals evidence of mediastinitis.
- There is presence of least one of the following signs or symptoms: fever (>38C), chest pain, or SI.

Moreover, at least one of the following criteria should be met:

- Purulent drainage from the mediastinal area.
- Mediastinal widening on imaging (Abu-Omar et al., 2017).

SWI can also be divided into “superficial” and “deep” infections, based on the depth of the infection. Early infections include “superficial” infections, reaching the dermis and subcutaneous tissue, and deep infections, reaching the sternum and the anterior mediastinum. Thus, a deep SWI can present as either an “early”—more common—or a “late” infection. Late infections often comprise a combination of superficial and deep infections and include osteomyelitis, subcutaneous abscess and sternocutaneous fistulas (Abu-Omar et al., 2017).

Table 1 Classification of mediastinitis according to El Oakley and Wright (Schimmer et al., 2007)

Type	Description
I	Mediastinitis presenting within 2 weeks after surgery in the absence of risk factors
II	Mediastinitis presenting at 2–6 weeks after surgery in the absence of risk factors
IIIA	Mediastinitis type I in the presence of one or more risk factors
IIIB	Mediastinitis type II in the presence of one or more risk factors
IVA	Mediastinitis type I, II, or III after one failed therapeutic trial
IVB	Mediastinitis type I, II, or III after more than one failed therapeutic trial
V	Mediastinitis presenting for the first time > 6 weeks after surgery

1.5.3. Risk factors

The pathogenesis of mediastinitis is complex and multifactorial. Several risk factors have been identified, among which diabetes and obesity are the most important. Furthermore, preoperative, intraoperative and postoperative variables have been described.

The preoperative risk factors include chronic obstructive pulmonary disease (COPD) (Rupprecht & Schmid, 2013), heart failure, left ventricular dysfunction, smoking, female sex, elevated serum creatinine level, hemodialysis, peripheral vascular disease, prolonged preoperative hospital stay, and emergent or urgent surgery.

The intraoperative risk factors include BIMA grafts use, prolonged duration of surgery, perfusion time, aortic cross-clamp time, redo cardiac surgery and reoperation.

The postoperative risk factors include postoperative respiratory failure and prolonged intensive care unit stay (Abu-Omar et al., 2017).

1.5.4. Diagnosis

The signs and symptoms of mediastinitis typically present within 30 days of cardiac surgery. The local signs include purulent drainage from the sternal wound and SI. In general, patients present with fever and elevated levels of inflammatory markers and show slow or no recovery. One of the most reliable signs of deep SWI is SI, which can be easily observed on

physical examination and is often reported by patients themselves (Francel, 2004). It may be difficult to distinguish between deep SWI and superficial SWI on physical examination. When a high index of suspicion is present, early wound opening and inspection with appropriate tissue sampling for bacteriological assessment are strongly advised.

Radiographic imaging can support clinical diagnosis and is included in the CDC guidelines for diagnosing mediastinitis. A simple posteroanterior chest radiograph can show the presence of air between sternal edges. Furthermore, lateral displacement of one or more sternal wires can be an indirect sign of a fractured or separated sternum. Computed tomography (CT) provides excellent details and is the investigation of choice when a diagnosis cannot easily be established by clinical examination alone. It is also valuable for making decisions regarding surgical planning. The typical CT findings in cases of mediastinitis are sternal disruption, free gas bubbles underneath the sternal plate and mediastinal fluid collection (Abu-Omar et al., 2017).

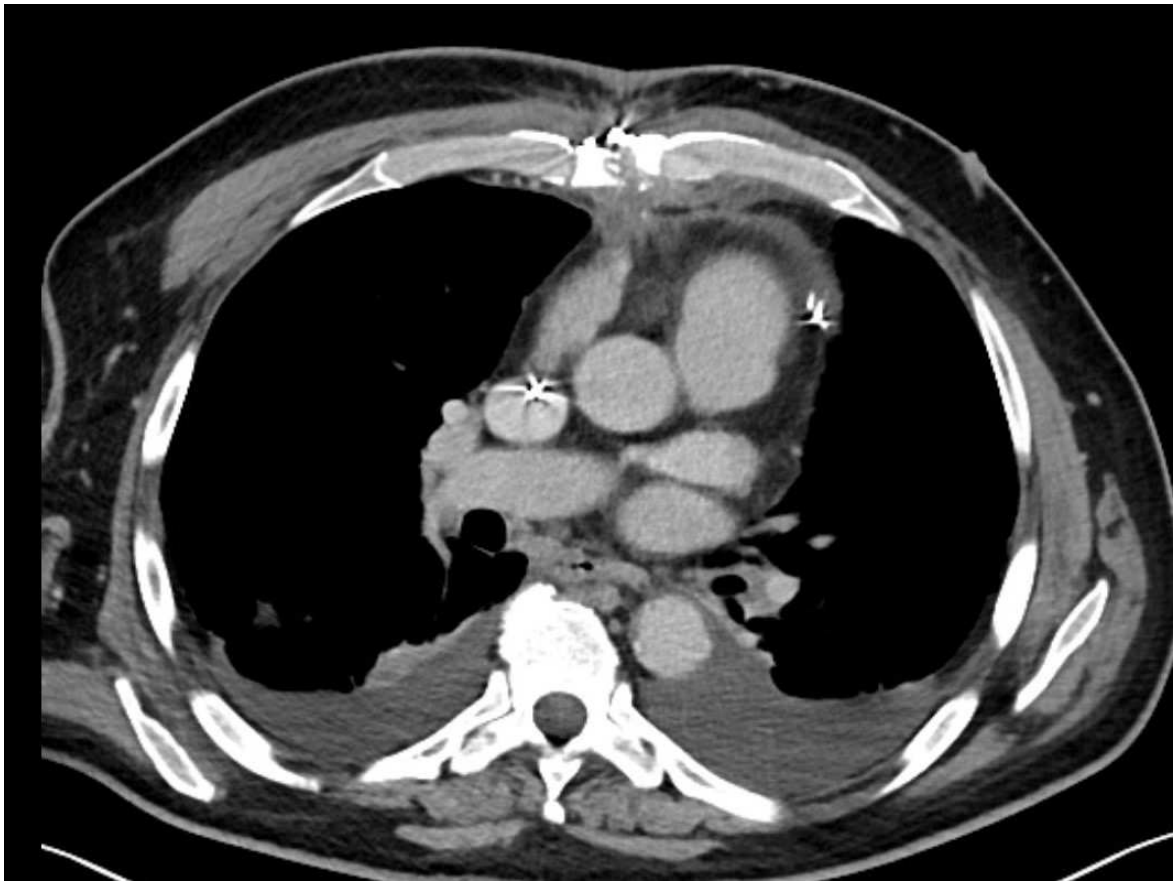

Figure 4 Chest CT axial view showing sternal dehiscence, retrosternal infiltration and pleural effusion on both sides. (Image Source: Wound clinic, Heart Centre Dresden)

1.5.5. Bacteriology of sternomediastinal fluid and tissues

The bacteriological spectrum of SWIs mainly includes *staphylococci* and the ratio between coagulase-negative and coagulase-positive staphylococci varies; however, the *staphylococcus aureus* is the most common bacteria. The other important bacteria include *Enterobacter spp., Enterococcus spp.,* and *Pseudomonas aeruginosa* (Abboud et al., 2004a; Borger et al., 1998; Eifert et al., 2007; Gummert et al., 2002).

Lepelletier et al. reported that among the 38 surgical site infections (SSI) cases, 28 (74%) cases showed positive cultures. The most commonly isolated pathogen was *Staphylococcus*, which caused 75% (21 of 28) infections. Gram-negative organisms *(Enterobacteriaceae)* were the responsible pathogens in seven (18%) cases. No polymicrobial infections were observed (Lepelletier et al., 2005)

Abu-Omar pointed out the significance of nasal carriage of *S. aureus*. The anterior nares are the most common areas for *S. aureus* colonization. Approximately 20% of the general population is persistently colonized, 30% is an intermittent carrier and the remaining 50% do not appear to be susceptible to *S. aureus* carriage for unclear reasons (Abu-Omar et al., 2017).

1.5.6. Osteomyelitis

Chronic poststernotomy osteomyelitis is observed in approximately 1%–5% patients and has been reported weeks, months, and years after sternotomy (Tan et al., 2016). The sentinel event of the pathogenesis is debatable. The proposed causes include the spread of pathogens via the direct spread of local infections and hematogenous dissemination (Toccoa et al., 2013). Regardless of the inciting event, bacteria invade the metaphyseal arterioles and cause microabscess formation, which eventually coalesces into larger macroabscesses, resulting in pressure erosion of the surrounding bone, which leads to necrosis (Hota et al., 2018).

Several organisms have been implicated in the development of poststernotomy osteomyelitis. Coagulase-negative *Staphylococcus* species are the most common, present in 65% patients in one retrospective analysis (Toccoa et al., 2013).

In combination with *S. aureus*, coagulase-negative *Staphylococcus* organisms account for 70%–80% pathogens. Multidetector CT (MDCT) offers superior bone resolution compared to other imaging modalities. The reported sensitivity for detection of osteomyelitis is 92.8% -

93.5%, and the specificity is 85.1% - 96%. MDCT readily allows the evaluation of areas of cortical erosion and destruction manifesting as irregular contours at the sternotomy site. It is also useful for the assessment of the bony sequestrum and involucrum (Hota et al., 2018).

Radiological diagnosis of sternal osteomyelitis is based on several imaging features that can be visualized on CT, although its exact sensitivity is unknown owing to a lack of dedicated studies. Sternal osteomyelitis is often accompanied by sternal nonunion and/or sternal dehiscence, which can be easily visualized on CT. If the bone marrow is replaced by a fluid collection containing gas bubbles, osteomyelitis is very likely. Furthermore, CT can reveal bone erosion, periosteal reactions, areas of sclerosis, and soft tissue swelling (Friebe et al., 2017).

1.6. Sternal fixation and wiring techniques

Different techniques can be used to close the sternum after surgery. Currently, the European and American cardiothoracic societies provide no guidelines for the uniform osteosynthetic method for primary sternal closure, and there is substantial variation in the perception of risk factors for SI and possible surgical consequences among surgical heart centers in Germany (Schimmer et al., 2006).

Wiring using stainless steel has been the standard technique for sternal closure since 1957 owing to its simplicity, strength, short healing time, and rigidity (Alhalawani & Towler, 2013). This technique is the most popular closure technique for primary sternotomy among surgeons (87% cases) (Schimmer et al., 2006).

The only cohesive force acting on the reunited sternum in the initial early postoperative period is the holding power of the sternal sutures. This is determined by several factors including the strength, number, and location of the sutures as well as the tightness and applied stress (force/area) exerted. If the wires cut into the sternum after they are tied, the sutures will loosen, and the sternum halves will first separate moderately. Then, due to the respiratory motion of the chest wall, the loose wires will literally cut the sternum into segments. Vigorous coughing and sneezing can exacerbate this process (Schimmer et al., 2006)

The results of different biomechanical clinical studies aimed at identifying the “the best” wiring technique are contradictory (Losanoff et al., 2004). An ideal procedure should consider a device that imparts suitable mechanical properties, radiopacity, biocompatibility,

removability when necessary, and cost effectiveness. Table 2 summarizes the criteria for such a device.

Table 2 Characteristics of a perfect adhesive cement and/or fixation device for robust sternal fixation (Alhalawani & Towler, 2013)

Criteria	Purpose
Mechanical properties	To withstand the maximum forces imposed during coughing and sneezing.
Radiopacity	To observe sternal displacement.
Biocompatibility	To avoid infection, rejection or inflammatory reaction.
Handling properties	To reduce operation time and achieve rigid fixation.
Removable when necessary	To facilitate revision surgery if necessary.
Cost effectiveness	To avoid limitations on use and supply.

1.7. Overview of sternal closure techniques in Germany

In a survey conducted in 2006 in Germany, Schimmer et al. obtained answers from all 79 German surgical heart centers. In total, 21/ 79 (27%) clinics stated that they used the transsternal closure technique as the conventional method for primary sternal closure. Further,11/79 (14%) heart centers stated that they used peristernal sutures. This method uses the compacta of the lateral table of the sternum as a reinforcement force, which may reduce the likelihood of the wires cutting through. Moreover, 18/79 (23%) clinics used alternating trans/peristernal sutures, and 9/79 (11 %) and 15/79 (19%) clinics applied the figure-of-eight sutures alone and in combination with transsternal sutures respectively. Most responding institutions (69/79 [87%]) used surgical stainless steel sutures, 6/79 (8%) used a combination of surgical stainless steel sutures and bands, and 5% used steel sutures and bands in combination with PDS sutures for primary sternal closure.

The number of sutures was 6–8 in 43/79 (54%) institutions. In total, 12/79 (15%) used 8–10 sutures, and 9/79 (11%) clinics used 4–6 sutures. Further, 4/79 (5%) surgical heart centers answered that they used one surgical stainless steel suture per 10 or 12 kg. When questioned about the reasons for modifying the standard osteosynthesis, the most commonly mentioned factors were alterations of the sternum (osteoporosis, 38 times; transverse fractures of the sternum, 32 times; and obesity 31 times). The preferred osteosynthetic procedure for patients with an increased risk of SI was described by Robicsek (48 ×). Eleven institutions stated that their usual osteosynthesis method was applied in all cases , without modification (Schimmer et al., 2007).

1.7.1. Sternal closure technique in Heart Center Dresden

In Dresden, we used an interlocking multitwisted wire technique as described by Casha. et al. Stainless steel no. 6 wire sutures in patients weighing < 100 kg or no. 7 wire sutures in patients weighing > 100 kg were used for sternal closure. The initial placement of wire sutures was identical to that of traditional sternal closure. All wires were placed approximately 1.5 cm from the sternal edge, or parasternally in the narrow sternum. Eight such wires were placed, five in the body of the sternum and three in the manubrium. The wires were Approximated by twisting the adjacent wire ends. No tension was required at this stage; however, it was important to keep the twisted portion of the wires equidistant from where they emerged from the sternal part.

The contralateral ends of the adjacent wires were then hand-twisted under tension causing the inner table of the sternal edges to come together. To aid in this, an assistant approximated the sternum using other wires. It was important to keep the twisted portion of the wires equidistant from where they emerged from the bone. The two twisted ends of the wires were then twisted together, further applying tension on all portions of the interlocking multitwisted wires. The resultant twisted four-strand portion was then bent 90° to lie along the surface of the sternum. Absorbable sutures were used to close the wound in the layers. These wires could be removed quickly and simply by cutting the two wires on one side of the sternum. Then, the wire could be easily removed by pulling the central four-stranded portion (Casha et al., 1999).

1.8. ASEPSIS score

For wound surveillance programs and clinical trials, a wound scoring method, ASEPSIS, assess wound sepsis more objectively and reproducibly by allotting points for the appearance of the wound in the first week and for the clinical consequences of infection (table 3, 4, und 5). Fixed criteria are necessary to provide some objectivity to wound surveillance or clinical trials of prophylactic procedures (Wilson et al., 1990).

Table 3 The ASEPSIS wound score (Tekalkote & Hussein, 2018)

Wound characteristic	Proportion of wound affected (%)					
	0	<20	20-39	40-59	60-79	>80
Serous exudates	0	1	2	3	4	5
Erythema	0	1	2	3	4	5
Purulent exudates	0	2	4	6	8	10
Separation of Deep tissues	0	2	4	6	8	10

Table 4 Criteria for allocation of additional points to ASEPSIS score (Tekalkote & Hussein, 2018)

Criterion	Description	Points
An Additional treatment	Antibiotics	10
	Drainage of pus under local anesthesia	5
	Debridement of wound (General anesthesia)	10
S Serous discharge	Daily	0-5
E Erythema	Daily	0-5
P Purulent exudates	Daily	0-10
S Separation of deep tissues	Daily	0-10
I Isolation of bacteria		10
S Stay in hospital prolonged over 14 days		5

Table 5 Category of infection (Gibbons et al., 2011)

Score range	Category
0-10	Wound healed satisfactorily
11-20	Disturbance of healing
21-30	Minor wound infection
31-40	Moderate wound infection
≥ 41	Severe wound infection

1.9. Nickel allergy/suture material allergy and biocompatibility

The use of metals in medicine has increased over the past few decades. Patients are exposed to metals in several ways, ranging from external exposure to instruments, such as stainless steel in surgical blades, to internal exposure via medical devices implanted in their bodies. There has been a growing interest in hypersensitivity reactions, both cutaneous and systemic to metals used in implanted medical devices. Although uncommon, hypersensitivity reactions to metals occur and require appropriate evaluation and management, particularly if they are symptomatic. The association between metal implants and metal sensitivity is well documented, although reactions are relatively unpredictable, poorly understood, and highly debated. Dermal hypersensitivity to metals is common and can affect up to 15% of the population. The insertion of metallic implants has been linked to hypersensitivity reactions, generally type IV delayed-type hypersensitivity reactions (Teo & Schalock, 2016).

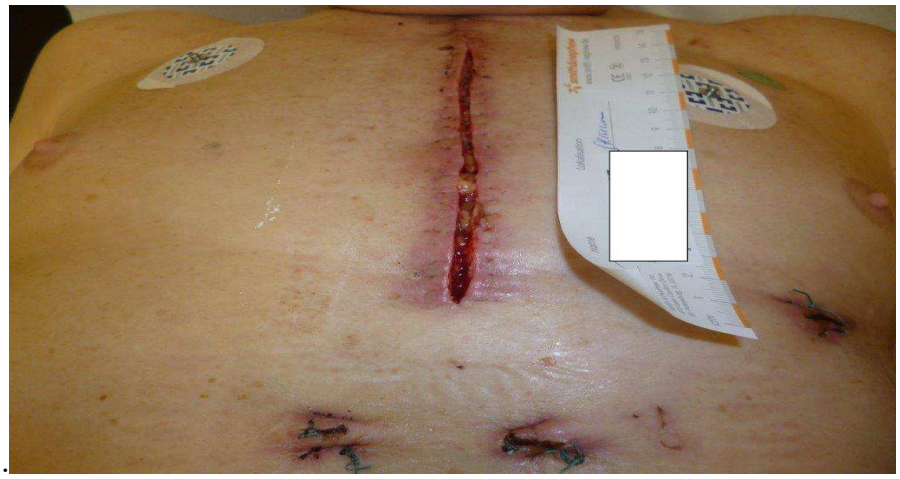

Figure 5 A post coronary artery bypass grafting patient showing hypersensitivity reaction / Intolerance to skin nickel staplers. (Image source: Wound clinic, Heart Center Dresden)

Nickel is the most common contact allergen and cause of contact allergy, particularly in women. The incidence of nickel allergy is 3-10 times higher in women than in men. A population-based study conducted in Germany reported sensitization rates of 20.4% in women and 5.8% in men. A recent study conducted in Denmark reported a prevalence of 10.4%, which was also significantly higher in women (14.4%) than in men (3.2%). It is estimated that approximately 65 million people in Europe are sensitized to nickel. This sex difference is traditionally justified by increased exposure to direct skin contact with nickel-releasing metals, such as jewelery, wristwatches, or clothing (Teo & Schalock, 2016).

Jewelry and wristwatches contain 9% - 28% nickel. Stainless-steel wires contain 17%–19% chromium and 13%–15 % nickel. Titanium wires are basically cobalt, nickel, and chromium free. The threshold for nickel sensitization is based on nickel release rather than nickel content, in other words, there is no correlation between the amount of nickel present in the alloy and the amount of migration. To release nickel from metallic nickel or nickel alloys, the nickel metal must be corroded, and the corrosion product dissolved into Ni^{2+}. Therefore, sweat or other wet conditions can increase the release rate compared to dry conditions (Buxton et al., 2019).

1.10 Nickel allergy and cardiac surgery

Allergic reactions to metals are well described in traumatology and odontology practice however, few cases have been reported in cardiac surgery (Dominguez-Massa et al., 2018). The reported cases of nickel allergy correlated with the use of stainless steel wires, presenting with pruritus, sternal pain, chronic tissue overgranulation, wound nonhealing, erythema, and osteomyelitis. Removal of sternal wires in these patients resulted in improvement or complete resolution of symptoms. More severe complications of nickel allergy, such as pericarditis and pericardial tamponade have been reported in patients after atrial septal defect closure using devices containing nickel, such as the Amplatzer (St. Jude Medical, Inc, Saint Paul, MN, USA) septal occluder device. The other nonspecific symptoms, such as migraines, chest pain, palpitations, and dermatitis, have also been documented in these patients and require surgical removal of the device (Zywicka et al., 2019).

Zywicka et al. (2019) reported severe systemic inflammatory response and cardiac tamponade due to edema of mediastinal tissues in a 48-year-old woman with a history of contact allergy to metal who underwent elective coronary artery bypass grafting postoperatively. No pericardial clots or fluid was observed. All cardiac and mediastinal tissues were extremely edematous, and mediastinal tissues were compressing the right ventricle. The patient required removal of stainless steel wires and delayed sternal closure with Ethibond sutures (Ethicon, Somerville, NJ) in addition to intravenous steroid therapy. Dominguez-Massa et al. (2018) reported a case of a 56-year-old man who presented with persistent urticarial rash and anaphylactic shock after mitral valve repair. The Department of Allergy performed multiple prick tests, which revealed nickel positivity. After removal of the nucleus from the mitral annulus, the urticarial rash disappeared.

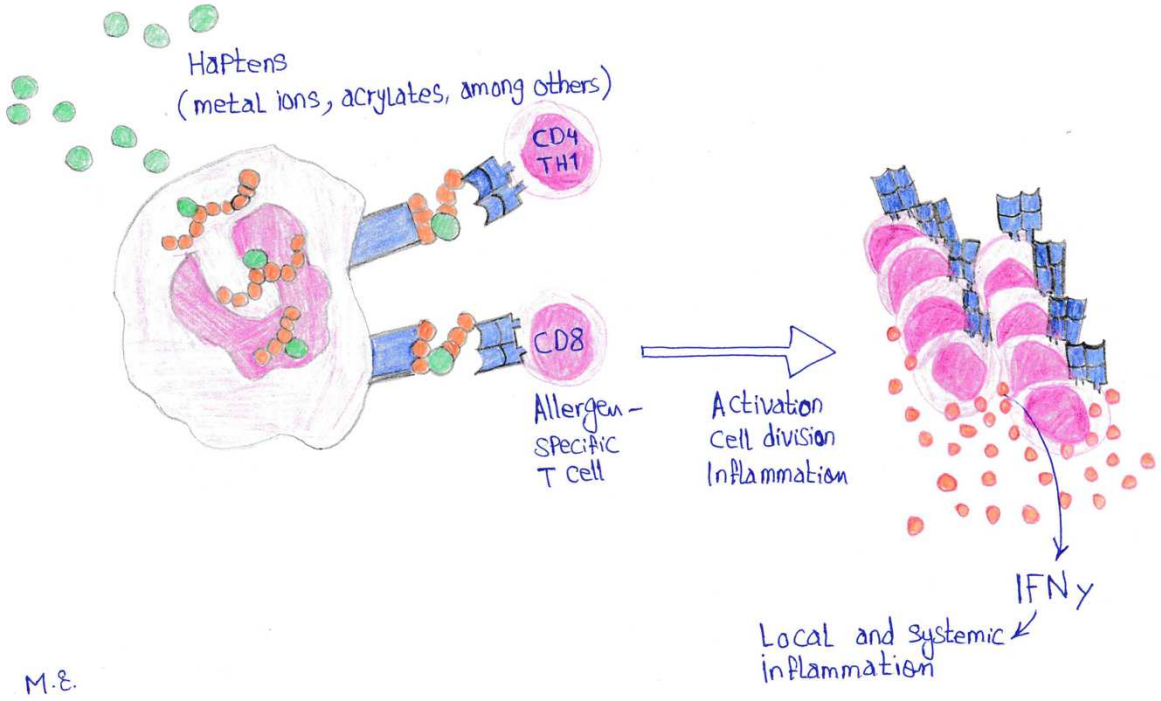

Figure 6 Type IV, hypersensitivity on contact with allergens

1.11. Titanium allergy

Putative hypersensitivity to titanium has been critically discussed by several researchers. The incidence of titanium hypersensitivity or allergy is unknown, and discussion on its existence is ongoing. Goutam et al. performed a literature review of reported cases of hypersensitivity to titanium. Limited reports on titanium allergy associated with titanium implants have been published (e.g impaired healing of fractures, pain, necrosis, and weakening of orthopedic implants). However, titanium allergy appears to be possible. As an explanation, Goutam et al. described that titanium ions can concentrate in tissues surrounding the implants. In their ionic form, metals can bond with native proteins to form haptenic antigens or trigger the degranulation of mastocytes and basophils, which are capable of inducing type I or IV hypersensitive reactions. However, evaluation of skin sensitization in mice and guinea pigs has shown that a significantly large amount of titanium ions is required to elicit a skin reaction. These results may explain the rarity of contact sensitization to titanium (Goutam et al., 2014).

In general, the cytotoxicity of metallic materials is the result of corrosion and the release of metal ions. Therefore, the cytotoxic effects of metallic materials were investigated using

L929 mouse fibroblasts using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide assay. Titanium grade 4 exhibited a cell viability of 99%. These results are in accordance with those published in the literature as titanium is widely used in orthopedic and dental implants because it is inert and corrosion resistant. Cytotoxicity, allergies and other biological effects are considered negligible (Gülçe Iz et al., 2010).

1.12. Pathophysiology of metal hypersensitivity reactions

Metal sensitization in nonsensitized individuals may result from a hypersensitive response to metal ions released from metallic implants. This is evidenced by the elevated levels of a range of immune cells and markers found in peri-implant tissue at various time intervals after implantation, including $CD3^+$ and $CD4^+$ T lymphocytes, $CD11c^+$ macrophages/dendritic cells, and cells with abundant expression of MHC class II (human leukocyte antigen-DR and dendritic cells) (Katou et al., 1996; Torgersen et al., 1995). In addition, significant levels of metal ions can be found in various parts of the body, including capsular and periprosthetic tissues and distant organs (such as the liver, the spleen, and lymph nodes), and in the urine and serum of patients undergoing total hip arthroscopy (Teo & Schalock, 2016).

Metal ions can be released via three possible mechanisms—mechanical wear; physiochemical corrosion when the implant comes into contact with biological fluids, such as sweat and the blood; and cellular-gated mechanisms, where it is unclear whether mature osteoclasts can corrode the metal surface (Teo & Schalock, 2016). Cadosch et al. demonstrated that osteoclast precursors can grow and differentiate on stainless steel, aluminum, and chromium in vitro and can directly corrode the metal surface and release metal ions (Cadosch et al., 2009).

The types of metallic ions that are released are dependent on the metallic composition of the implants—stainless steel devices release iron, chromium, molybdenum, and nickel ions, whereas titanium devices release titanium (IV), vanadium, and aluminum ions. Among the different alloys, standard stainless steel releases the most Ni ions. Exposure to metal ions triggers various local and remote immune responses (Teo & Schalock, 2016).

Both local and systemic immune reactivity to metal ions are likely to be driven by adaptive immunity via type IV, delayed-type reactions, in which cells necessary for the development of T cell-mediated type IV hypersensitivity often affects perivascular tissue next to stainless steel or titanium implants. The typical pathological features of a type IV hypersensitivity reaction are heavy perivascular lymphocytic infiltrate, macrophage response, and granuloma formation with tissue necrosis (Teo & Schalock, 2016).

An ideal biomaterial should exhibit properties such as very high biocompatibility; in other words, it has no adverse tissue response. In addition, it should have a density as low as that of bone, a high mechanical strength and fatigue resistance, a low elastic modulus, and good wear resistance. It is very difficult to combine all these properties into a single material (Oldani & Dominguez, 2012).

The principal disadvantage of metals is their tendency to corrode in vivo. Most metals can only be tolerated by the human body in small amounts, even when present as metallic ions. The consequences of corrosion are disintegration of the material implant, which weakens the implant, and the harmful effect of corrosion products on the surrounding tissues and organs (Oldani & Dominguez, 2012).

Stainless steel is a good material for metal implants and is often used in trauma surgery. These implants are characterized by good mechanical properties (stiffness, ductility, and elasticity), ease of production, and low cost. However, stainless steel implants have lower resistance to corrosion than other implants, such as titanium implants. In addition, biocompatibility is not optimal, primarily because of the nickel content and the potential for an allergic reaction. Biocompatibility is achieved when the functionality of an implant is achieved without eliciting a foreign body reaction within the tissue. Owing to these features, stainless steel is currently only used in temporary implants (Plecko et al., 2012).

Titanium and titanium alloys exhibit high specific strength, which makes them an excellent choice for biomedical applications. Furthermore, titanium is considered biocompatible because it has a low electrical conductivity, which contributes to the electrochemical oxidation of titanium, leading to the formation of a thin passive oxide layer. In turn, the oxide layer leads to high resistance to corrosion. This protective passive layer is retained at pH values of the human body because titanium has an oxide isoelectric point of 5–6. In aqueous environments, titanium and its oxides have low information tendency and low reactivity with macromolecules (Sidambe, 2014).

Commercially pure titanium and extra low interstitial Ti-6Al-4V are the two most common titanium-based implant biomaterials. These materials are classified as biologically inert. Therefore, they remain essentially unchanged when implanted into the human body. The human body can recognize these materials as foreign and try to isolate them by encasing them in fibrous tissue. However, they do not promote any adverse reactions and are well-tolerated by human tissues. However, these metals do not induce allergic reactions. Their excellent biocompatibility is attributed to the formation of an oxide film (TiO_2) on its surface.

This oxide forms a strong and stable layer spontaneously when it comes in contact with air and prevents the diffusion of oxygen from the environment (Oldani & Dominguez, 2012).

1.13. Hypothesis of the study

The current knowledge is that the use of a titanium wire has no advantage in terms of the incidence of sternal instability and wound infection after median sternotomy in patients undergoing cardiac surgery if there is no nickel allergy. In other words, titan wire is inferior to stainless steel wire. This study aimed to demonstrate the non-inferiority of titanium wires even in patients without a known allergy.

2. Materials and methods

This randomized controlled prospective single-blinded study (parallel design) included 322 patients who underwent elective cardiac surgery between October 2019 and October 2020 at Heart Center Dresden, Technical University of Dresden. The Ethics Committee of University of Technology, Dresden, Germany, approved this study in June 2019 (EK 287062019). Informed written consent was obtained from all patients.

The participants were randomly divided into two groups of 161 participants each according to the sternum wire closure method— study group (titanium wires) and comparison group (stainless steel wires).

2.1. Study population

2.1.1. Inclusion criteria

All patients undergoing elective median sternotomy and provided written informed consent were included.

2.1.2. Exclusion criteria

- Redo median sternotomy
- Presence of infection as infective endocarditis
- Early postoperative re-exploration due to postoperative bleeding
- Participation in another interventional trial
- Emergency operation
- Corticosteroids or immunosuppressive therapy such as methotrexate therapy
- History of pathological sternal fracture
- Pregnancy and lactating

All patients were admitted one day before surgery and received the following treatment according to our protocol: prophylactic IV cefuroxime 1.5 g or 3 g based on body weight (>80 or <80 kg) at the time of induction of anesthesia and repeated after termination of cardiopulmonary bypass.

2.2. Intervention

Titanium wires (FSSB Chirurgische Nadeln GmbH) were used.

2.3. Control

Stainless steel wires (FSSB Chirurgische Nadeln GmbH) were used as the standard wires in Heart Center Dresden.

2.4. Outcome

i- Primary endpoint: incidence of postoperative sternal instability

ii- Secondary endpoints: severity of wound infection (according to the CDC classification), ASEPSIS score for assessing the severity of the wound (score: 0–40), and pain rating score for assessing the individual pain impression

2.5. Time

The duration of the study was 1 year, and the postoperative follow-up period was 3 months for each patient.

2.6. Sample Size calculation

Considering an alpha of 0.05 (alpha = level of significance/type I error) and a power of 0.8 (1-ß = power, ß = type II error), the estimated effect size based on our clinical experience to identify the noninferiority margin using a minimal clinical significance difference (MCSD) between the treatment groups was 10%–12%, which was calculated using a two-sided test with the chi-square test for comparing two independent proportions and categorical outcome (SI). The drop-out rate was <5% as all patients in the early postoperative period according to the standard of post-operative care in Germany are adherent to the wound clinic of the operating cardiac center. In addition, sensitivity analysis was performed to manipulate the MCSD range. In total, 131–177 patients should be included in each group.

Due to the lack of a previous pilot study and lack of appropriate analogies to our study in the literature, a clinical judgement was used to set the noninferiority margin.

Alpha	Power	N	N1	N2	Delta	P1	P2
0.05	0.8	354	177	177	0.1	0.08	0.18
0.05	0.8	262	131	131	0.12	0.08	0.2

2.7. Sternal closure technique

The sternum was closed using either no. 6 or no. 7 steel wire or no. 7 titanium sutures on a taper cut needle. In both groups, closure was performed using an interlocking multitwisted technique using eight sutures, as shown in Figure 7.

The first three sutures or wires were inserted through the manubrium (1.5 cm), lateral to the midline. The remaining five sutures or wires were inserted transsternal/peristernal in the body of the sternum. The two adjacent free ends of the wire on each side were twisted together, and then twisted again with the twisted-free ends on the other side (multiple twists, 2 × 4). Using the rotary movement of the wrist along with a vertical pull on the wires, the wires were twisted tightly until the two bone edges were approximated. Subcutaneous tissues were closed in one interrupted layer using 0 Ethicon VICRYL (Ethicon Inc., a subsidiary of Johnson and Johnson), and the skin edges were approximated subcuticularly with Ethicon Monocryl suture USP 3/0.

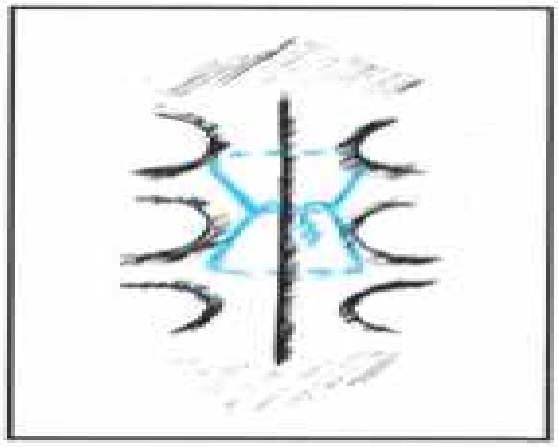

Figure 7 Multitwist sternal wiring technique (Loladze et al., 2017)

On the third postoperative day and seventh or first day before the discharge, to exclude any confounding pain that might have been caused due to the presence of the chest tubes, the patients were assessed for surgical site pain at least three times daily (before administering analgesics). Further, they were assessed when they complained of pain. The pain score was calculated using the 0–10 numeric pain rating scale.

The pain was graded as mild, moderate, or severe. For analysis (Table 6), the highest daily pain score for each patient was considered. After pain assessment, all patients received the

same standard pain killers—tramadol 100 mg twice daily and metamizol 30–40 drops maximum five times daily as needed. The wounds were assessed daily by nursing staff. Consultation with our wound clinic team was sought if there was any suspicion or early signs of wound infection.

The wound was inspected for erythema, serous or purulent discharge, separation of deep tissue, and SI. Cultures were performed using samples from discharged wounds, and bacterial growth was identified. The main investigator calculated ASEPSIS scores.

The following well-known potential risk factors for postoperative surgical site infection were considered:

Preoperative factors: age, sex, body mass index (BMI), logistic Euroscore II, smoking, COPD, peripheral vascular disease, renal insufficiency, and diabetes mellitus

Intraoperative factors: single or bilateral left internal mammary harvesting, aortic cross-clamp time, cardiopulmonary bypass time, and operation time

Postoperative factors: duration of mechanical ventilation, re-intubation, delirium, and renal insufficiency

Table 6 Grading of pain according to the numeric pain rating scale

0	No pain
1–3	Mild pain (nagging, annoying, and interfering little with ADL)
4–6	Moderate (interfering significantly with ADL)
7–10	Severe (disabling and unable to perform ADL)

ADL: activities of daily living

2.8. Handling of the wire

Both wires were comparable in terms of surgical handling. According to our experience of using both wires regularly for 1 year (time of our study), there are two main technical differences:

a- The needle of the titanium wire has more penetration power; in other words, it is sharper, which is very helpful, especially when the sternum is markedly thick.
b- In inexperienced hands, a titanium wire can be broken if the twist is tightly applied. This implies that titanium is less stiff than steel.

2.9. Blinding and randomization technique

Double blinding is not possible because the surgeon recognizes the type of wire when the sternum is closed. Patients and ward nurses, who assessed the degree of postoperative pain according to the pain rating scale, were blinded. Neither the data collector/main investigator nor the statistician were blinded. Regarding randomization, patients who underwent surgery on even days received stainless steel wire, while those who underwent surgery on odd days received titanium wire. Both the chief operating nurse and main investigator took responsibility for the randomization technique (allocation concealment).

2.10. Data collection and documentation

Data collection was performed during the entire in-hospital stay of patients and rehabilitation. The postoperative observation period was 3 months. To ensure the validity of the clinical results, data were collected from several sources—patient files, internal and external medical reports, anesthesia protocols and protocols from the normal surgical ward, intermediate care (IMC), intensive care unit, and our wound clinic.

For documentation purposes, considering data confidentiality, a questionnaire was created in Microsoft Excel, in which the relevant patient parameters were systematically recorded.

2.11. Statistics

Statistical analyses were performed using SPSS for Windows (version 26.0, SPSS Inc., USA). Continuous variables are presented as mean values, whereas the measures of dispersion are presented as standard deviations.

Continuous variables were measured using the Shapiro–Wilk test to check for normal distribution. Although the distribution of some of the variables tested was non-normal ($p \leq 0.05$), the other variables showed a normal distribution ($p > 0.05$).

For normally distributed samples, the two independent samples t-test was used. For samples that were not normally distributed, the Mann–Whitney U test was used as a nonparametric method. Categorical data were compared using the chi-square test. Univariate analysis was used for the nominal variables.

Binary logistic regression with forward inclusion was used for multivariate analysis using the likelihood ratio criterion (inclusion $p \leq 0.05$; exclusion $p > 0.1$).

A two-sided significance check was performed for all tests, where a p-value of ≤ 0.05 was considered statistically significant for all statistical tests.

3. Results

A total of 322 patients were included. The postoperative follow-up time was 3 months. To evaluate the effect of wire type on the incidence of postoperative SI, we first checked the extent to which the two groups were affected. There was no statistically significant difference between the two groups regarding population characteristics and risk factors for our primary endpoints.

The only significant difference between the groups in terms of results was postoperative pain on the third and seventh days (Table 12).

3.1. Preoperative parameters

3.1.1. Entire group

Among the included patients, 18.9% were women (n = 61) and 81.1% (n = 261) men.
The average age of the patient at the time of surgery was 68.7 ± 9.2 years, with the youngest patient being 29 years old and the oldest patient being 86 years old. The mean BMI was 28.2 ± 4.6 kg/m^2. Further, 126 (39.1%) patients had diabetes mellitus. The other preoperative parameters for the entire group are shown in Table 7.

Table 7 Epidemiological parameters of the entire group (baseline characteristics of all patients)

Parameter	n = 322
Sex	
Men	261 (81.1%)
Women	61 (18.9%)
Age (years)	68.7 ± 9.2
BMI (kg/m^2)	28.2 ± 4.6
Euroscore	2.6 ± 2.6
Smoking	
No	248 (77.0%)
Yes	74 (23.0%)
COPD	
No	285 (88.5%)
Yes	37 (11.5%)
Peripheral vascular disease	
No	278 (86.3%)
Yes	44 (13.7%)
Diabetes mellitus	
No	196 (60.9%)
Diet	20 (6.2%)
Tablet	59 (18.3%)
Insulin	47 (14.6%)
Renal failure (GFR, ml/min)	73.6 ± 18.3
Wire	
Nickel (stainless steel)	161 (50.0%)
Titanium	161 (50.0%)

3.1.2. Group comparison

There were no preoperative significant differences in the risk profiles of both groups. The results are summarized in Table 8.

Table 8 Comparison of epidemiological parameters between the study and comparison groups

Parameter	Group 1 (titanium) n = 161	Group 2 nickel (stainless steel) n = 161	p-value
Sex			
Men	131 (81.4%)	130 (80.7%)	0.887
Women	30 (18.6%)	31 (19.3%)	
Age (years)	69.2 ± 8.8	68.2 ± 9.7	0.387
BMI (kg/m^2)	27.8 ± 4.3	28.7 ± 4.9	0.127
Euroscore	2.7 ± 2.6	2.6 ± 2.6	0.887
Smoking			
No	121 (75.2%)	127 (78.9%)	0.427
Yes	40 (24.8%)	34 (21.1%)	
COPD			
No	143 (88.8%)	142 (88.2%)	0.861
Yes	18 (11.2%)	19 (11.8%)	
Peripheral vascular disease			
No	142 (88.2%)	136 (84.5%)	0.330
Yes	19 (11.8%)	25 (15.5%)	
Diabetes mellitus			
No	92 (57.1%)	104 (64.6%)	
Diet	15 (9.3%)	5 (3.1%)	0.123
Tablet	30 (18.6%)	29 (18.0%)	
Insulin	24 (14.9%)	23 (14.3%)	
Renal failure (GFR, ml/min)	73.1 ± 19.2	74.1 ± 17.3	0.958

The proportions of male patients were 81.4% and 80.7% in the study and comparison groups respectively. The proportions of female patients were 18.6% and 19.3% in the study and comparison groups, respectively.

3.2. Intraoperative parameters

3.2.1. Entire group

The following table provides an overview of the intraoperative parameters of the entire group.

Table 9 Mammary artery, operative time, aortic clamp time, cardio-pulmonary bypass in the entire group

Parameter	n = 322
Mammary artery	
No	30 (9.3%)
LIMA	281 (87.3%)
BIMA	11 (3.4%)
Operation time (minutes)	167.9 ± 33.7
Aortic clamp time (minutes)	48.9 ± 20.4
Cardiopulmonary bypass (minutes)	67.3 ± 24.0

3.2.2. Group comparison

No statistically significant differences were found between the groups in term of intraoperative parameters (Table 10).

Table 10 Comparison of intraoperative parameters between the study and comparison groups

Parameter	Group 1 (titanium) n = 161	Group 2 (nickel [stainless steel]) n = 161	p-value
Mammary artery			
No	10 (6.2%)	20 (12.4%)	
LIMA	146 (90.7%)	135 (83.9%)	0.146
BIMA	5 (3.1%)	6 (3.7%)	
Operation time (minutes)	167.9 ± 33.7	168.0 ± 33.7	0.983
Aortic clamp time (minutes)	48.0 ± 19.5	49.8 ± 21.3	0.486
Cardiopulmonary bypass (minutes)	66.4 ± 22.7	68.2 ± 25.3	0.507

3.3. Postoperative parameters

3.3.1. Entire group

The following table presents the postoperative parameters of the entire group.

Table 11 Postoperative parameters of the entire group

Parameter	n = 322
Pain third day classification	
0 - 3	311 (96.6%)
> 3	11 (3.4%)
Pain seventh day classification	
0 - 3	317 (98.4%)
> 3	5 (1.6%)
Ventilation duration (hours)	8.2 ± 27.3
Reintubation	
No	322 (100.0%)
Yes	0 (0.0%)
Delirium	
No	272 (84.5%)
Yes	50 (15.5%)
Postoperative renal failure (GFR, ml/min)	70.2 ± 21.3
Sternal instability	
No	308 (95.7%)
Yes	14 (4.3%)
ASEPSIS Score	2.4 ± 9.5
Wound	
No	288 (89.4%)
Yes	34 (10.6%)
Antibiotic	
No	312 (96.9%)
Yes	10 (3.1%)
Pus drainage	
No	314 (97.5%)
Yes	8 (2.5%)

Wound revision	
No	307 (95.3%)
Yes	15 (4.7%)
Swab	
No	303 (94.1%)
Sterile	10 (3.1%)
Yes / positive	9 (2.8%)
Length of hospital stay > 14 days	
No	298 (92.5%)
Yes	24 (7.5%)
Mediastinitis	
No	317 (98.4%)
Yes	5 (1.6%)
Osteomyelitis	
No	315 (97.8%)
Yes	7 (2.2%)
Therapy result	
Unremarkable	287 (89.1%)
Conservative	20 (6.2%)
Secondary suture	6 (1.9%)
Rewiring	3 (0.9%)
Permanent VAC	0 (0.0%)
Plastic surgery in our department	0 (0.0%)
Discharged to the plastic surgery department	6 (1.9%)
ASEPSIS score classification	
0 – 40	314 (97.5%)
> 40	8 (2.5%)

3.3.2. Group comparison

Postoperatively, the number of patients with pain on the third and seventh days in group 1 (titanium wire) was significantly lower than that in group 2 (nickel wire) ($p = 0.032$ and $p = 0.024$, respectively).

Table 12 Comparison of postoperative parameters between the study and comparison groups

Parameter	Group 1 (titanium) n = 161	Group 2 (nickel [stainless steel]) n = 161	p-value
Pain third day classification			
0 - 3	159 (98.8%)	152 (94.4%)	0.032
> 3	2 (1.2%)	9 (5.6%)	
Pain seventh day classification			
0 - 3	161 (100.0%)	156 (96.9%)	0.024
> 3	0 (0.0%)	5 (3.1%)	
Ventilation duration (hours)	6.7 ± 6.7	9.6 ± 38.0	0.773
Reintubation			
No	161 (100.0%)	161 (100.0%)	_____
Yes	0 (0.0%)	0 (0.0%)	
Delirium			
No	136 (84.5%)	136 (84.5%)	1.000
Yes	25 (15.5%)	25 (15.5%)	
Postoperative renal failure (GFR, ml/min)	70.5 ± 21.9	69.8 ± 20.7	0.462
Sternal instability			
No	155 (96.3%)	153 (95.0%)	0.585
Yes	6 (3.7%)	8 (5.0%)	
ASEPSIS score	2.1 ± 9.4	2.8 ± 9.6	0.113
Wound			
No	148 (91.9%)	140 (87.0%)	0. 147
Yes	13 (8.1%)	21 (13.0%)	
Antibiotic			
No	156 (96.9%)	156 (96.9%)	1.000
Yes	5 (3.1%)	5 (3.1%)	
Pus drainage			
No	158 (98.1%)	156 (96.9%)	0.474

Yes	3 (1.9%)	5 (3.1%)	
Wound revision			
No	153 (95.0%)	154 (95.7%)	0.791
Yes	8 (5.0%)	7 (4.3%)	
Swab			
No	153 (95.0%)	150 (93.2%)	0.419
Sterile	3 (1.9%)	7 (4.3%)	
Yes / positive	5 (3.1%)	4 (2.5%)	
Length of hospital stay > 14 days			
No	153 (95.0%)	145 (90.1%)	0.090
Yes	8 (5.0%)	16 (9.9%)	
Mediastinitis			
No	159 (98.8%)	158 (98.1%)	0.652
Yes	2 (1.2%)	3 (1.9%)	
Osteomyelitis			
No	158 (98.1%)	157 (97.5%)	0.702
Yes	3 (1.9%)	4 (2.5%)	
ASEPSIS score classification			
0 – 40	156 (96.9%)	158 (98.1%)	0.474
> 40	5 (3.1%)	3 (1.9%)	

3.4. Incidence of postoperative SI

Fourteen cases of SI occurred postoperatively, which is 4.3% of the entire group (n = 322). In group 1 (titanium wire), 6/161 (3.7%) patients developed postoperative SI. In group 2 (nickel wire), 8/161 (5.0%) patients had postoperative sternal instabilities.

There was no statistically significant difference in the occurrence of SI between the groups.

3.5. Univariate analysis

Univariate analysis was performed in the entire group (n = 322), where the preoperative, intraoperative, and postoperative parameters of the patients with SI were compared with those of patients without SI.

3.5.1. Pre-operative parameters

Table 13 Influence of preoperative parameters on the development of postoperative SI (univariate analysis).

Parameter	Group 1 (SI = No) n = 308	Group 2 (SI = Yes) n = 14	p-value
Sex			
Men	250 (81.2%)	11 (78.6%)	0.808
Women	58 (18.8%)	3 (21.4%)	
Age (years)	68.7 ± 9.3	68.5 ± 6.8	0.722
BMI (kg/m^2)	28.1 ± 4.6	31.7 ± 4.4	0.002
Euroscore	2.6 ± 2.6	3.2 ± 3.0	0.458
Smoking			
No	237 (76.9%)	11 (78.6%)	0.888
Yes	71 (23.1%)	3 (21.4%)	
COPD			
No	274 (89.0%)	11 (78.6%)	0.233
Yes	34 (11.0%)	3 (21.4%)	
Peripheral vascular disease			
No	267 (86.7%)	11 (78.6%)	0.387
Yes	41 (13.3%)	3 (21.4%)	
Diabetes mellitus			
No	189 (61.4%)	7 (50.0%)	
Diet	20 (6.5%)	0 (0.0%)	0.358
Tablet	56 (18.2%)	3 (21.4%)	
Insulin	43 (14.0%)	4 (28.6%)	
Renal failure (GFR, ml/min)	73.5 ± 18.1	75.0 ± 22.9	0.391

3.5.2. Intra-operative parameters

Table 14 Influence of intraoperative parameters on the development of postoperative SI (univariate analysis).

Parameter	Group 1 (SI = No) n = 308	Group 2 (SI = Yes) n = 14	p-value
Wire			
titanium	155 (50.3%)	6 (42.9%)	0.585
nickel (stainless steel)	153 (49.7%)	8 (57.1%)	
Mammary artery			
No	29 (9.4%)	1 (7.1%)	
LIMA	268 (87.0%)	13 (92.9%)	0.731
BIMA	11 (3.6%)	0 (0.0%)	
Operation time (hours)	168.1 ± 33.8	165.4 ± 32.0	0.770
Aortic clamp time (hours)	49.1 ± 20.1	44.1 ± 28.2	0.428
Cardiopulmonary bypass (hours)	67.6 ± 23.7	62.1 ± 31.8	0.386

3.5.3. Post-operative parameters

Table 15 Influence of postoperative parameters on the development of postoperative SI (univariate analysis)

Parameter	Group 1 (SI = No) n = 308	Group 2 (SI = Yes) n = 14	p-value
Ventilation duration	8.3 ± 27.9	6.0 ± 3.6	0.855
Reintubation			
No	308 (100.0%)	14 (100.0%)	_____
Yes	0 (0.0%)	0 (0.0%)	
Delirium			
No	262 (85.1%)	10 (71.4%)	0.168
Yes	46 (14.9%)	4 (28.6%)	
Postoperative renal failure (GFR, ml/min)	70.3 ± 20.9	67.1 ± 28.8	0.960

3.5.4. Statistically significant data

Regarding the SI, the following parameters were statistically significant in univariate analysis:

• BMI (p = 0.002)

3.5.5. Descriptive presentation of subgroup analysis (SI and wire classification)

The following is descriptive statistics of SI cases.

3.5.5.1. Pre-operative parameters

Table 16 Comparison of the preoperative parameters of the study and comparison groups in patients with SI.

Parameter	Group 1 (titanium) n = 6	Group 2 (nickel [stainless steel]) n = 8	p-value
Sex			
Men	4 (66.7%)	7 (87.5%)	0.347
Women	2 (33.3%)	1 (12.5%)	
Age (years)	72.0 ± 4.7	65.9 ± 7.2	0.097
BMI (kg/m^2)	32.2 ± 5.3	31.3 ± 3.9	0.366
Euroscore	4.5 ± 3.6	2.3 ± 2.2	0.053
Smoking			
No	5 (83.3%)	6 (75.0%)	0.707
Yes	1 (16.7%)	2 (25.0%)	
COPD			
No	3 (50.0%)	8 (100.0%)	0.024
Yes	3 (50.0%)	0 (0.0%)	
Peripheral vascular disease			
No	5 (83.3%)	6 (75.0%)	0.707
Yes	1 (16.7%)	2 (25.0%)	
Diabetes mellitus			
No	2 (33.3%)	5 (62.5%)	0.017
Diet	0 (0.0%)	0 (0.0%)	
Tablet	0 (0.0%)	3 (37.5%)	
Insulin	4 (66.7%)	0 (0.0%)	
Renal failure (GFR ml/min)	66.8 ± 33.0	81.1 ± 9.8	0.264

3.5.5.2 Intra-operative parameters

Table 17 Comparison of the intraoperative parameters of the study and comparison groups in patients with sternal instability

Parameter	Group 1 (titanium) n = 6	Group 2 (nickel [stainless steel]) n = 8	p-value
Mammary artery			
No	0 (0.0%)	1 (12.5%)	0.369
LIMA	6 (100.0%)	7 (87.5%)	
BIMA	0 (0.0%)	0 (0.0%)	
Operation time (hours)	148.5 ± 32.0	178.0 ± 27.3	0.087
Aortic Clamp time (hours)	35.3 ± 21.9	50.6 ± 31.9	0.335
Cardiopulmonary bypass (hours)	53.2 ± 13.9	68.9 ± 40.3	0.382

3.5.5.3. Post-operative parameters

Table 18 Comparison of the postoperative parameters of the study and comparison groups in patients with sternal instability

Parameter	Group 1 (titanium) n = 6	Group 2 (nickel [stainless steel]) n = 8	p-value
Pain third day classification			
0 - 3	6 (100.0%)	7 (87.5%)	0.369
> 3	0 (0.0%)	1 (12.5%)	
Pain seventh day classification			
0 - 3	6 (100.0%)	8 (100.0%)	———
> 3	0 (0.0%)	0 (0.0%)	
Ventilation duration (hours)	7.5 ± 4.7	4.9 ± 2.3	0.131
Reintubation			
No	6 (100.0%)	8 (100.0%)	———
Yes	0 (0.0%)	0 (0.0%)	
Delirium			
No	4 (66.7%)	6 (75.0%)	0.733
Yes	2 (33.3%)	2 (25.0%)	
Postoperative renal failure (GFR, ml/min)	49.7 ± 32.7	80.3 ± 17.9	0.081

3.5.6. Logistic regression analysis

Multivariate analysis was performed to determine the simultaneous effects of several factors on SI. The aim was to identify the risk factors for developing SI. The target variable (SI) to be examined had a binary measurement level (SI yes/no); therefore, the logistic regression analysis was used as the evaluation method.

All preoperative, intraoperative, and early postoperative parameters that showed statistical significance in univariate analysis ($p < 0.05$) were tested in the binary logistic regression model as independent variables together with other parameters that could influence the target variable.

Logistic regression analysis resulted in an odds ratio (OR) for each independent variable, which indicates whether the risk increases or decreases.

OR = 1 indicates that the factor under consideration does not have any impact on the event.

OR > 1 indicates increased risk

OR < 1 indicate a decreasing risk

The results are summarized in the table below.

Table 19 Variables used in the multivariate analysis of risk factors for postoperative sternal instability.

		B	S.E.	Wald	df	Sig.	Exp(B)	95% CI for EXP(B)	
								Lower	Upper
Step 1[a]	BMI	0.140	0.051	7.674	1	0.006	1.151	1.042	1.271
	Constant	-7.270-	1.614	20.286	1	0.000	0.001		
a. Variable(s) entered in step 1: BMI									

Table 20 Variables not used in the equation

			Score	df	Sig.
Step 1	Variables	Sexr(1)	0.001	1	0.979
		Age	0.300	1	0.584
		Euroscore	2.324	1	0.127
		Smoking(1)	0.024	1	0.876
		COPD(1)	1.097	1	0.295
		Peripheral_vascular_disease(1)	1.618	1	0.203
		DM	2.361	3	0.501
		DM/diet	0.977	1	0.323
		DM/tablet	0.005	1	0.944
		DM/insulin	1.577	1	0.209
		Renal_failure_GFR	0.025	1	0.876
		Wire(1)	0.055	1	0.815
		Mammary_artery	0.711	2	0.701
		LIMA	0.577	1	0.447
		BIMA	0.446	1	0.504
		Ventilation_duration	0.084	1	0.772
		Delirium(1)	1.953	1	0.162
	Overall statistics		8.315	15	0.911

3.6. Summary/key results

In our study, BMI influenced SI (p = 0.006, OR = 1.151). The OR showed that higher BMI increased the risk of SI by a factor of approximately 1.15.

4. Discussion

The stainless steel wire is the standard wire in most cardiac centers worldwide, and it is well established; the standard wire is also used in our center. The titanium wire is less frequently used and its application is limited to only patients allergic to nickel; however, titanium is a well-established material for use in the medical field, including dental surgery and orthopedics. To the best of our knowledge, no prospective randomized or retrospective study has compared the two common sternal wires in cardiac surgery in terms of postoperative SI, wound infection, and postoperative pain.

We found that the titanium wire is comparable to the stainless steel wire in terms of postoperative SI, which was our primary outcome. The incidence of SI in all patients was 4.3%; 3.7% and 5.0% patients had study and comparison groups, respectively ($p = 0.585$).

This study also demonstrated for the first time similarities between the groups in terms of the incidence of postoperative wound infection. The total incidence of wound infection, including superficial or deep infection, in the entire group was 10.6%. The incidence of wound infection in comparison group (13%) was slightly higher than that in the study group (8.1%), whereas that of deep SWI (ASEPSIS score >40) was higher in study group (3.1%) than in the comparison group (1.9%); both differences were statistically nonsignificant, with a p-value of 0.147 and 0.474, respectively.

The incidence of mediastinitis in the entire group was 1.6%. There was no statistically significant difference between the groups in terms of mediastinitis, with incidence rate of 1.2% in the study group and 1.9% in the comparison group ($p = 0.625$).

In this study, there was lower postoperative pain on the third and seventh days in the study group than in the comparison group. The percentage of patients who experienced postoperative pain >3 on the numeric pain rating scale on the third day was 1.2% and 5.6% in the study and comparison groups, respectively ($p = 0.032$). This finding was confirmed on the seventh day, with an incidence of 0.00% and 3.1% in the study and comparison groups, respectively ($p = 0.024$). No postoperative pain of >7 on the numeric pain rating scale was recorded in either group.

Several factors increase the risk of postoperative SI. Univariate analysis showed that BMI is the only independent risk factor for SI, with mean BMI 31.7 ± 4.4 kg/m^2 among patients with SI and 28.1 ± 4.6 kg/m^2 for those without SI ($p = 0.002$). This positive finding was confirmed

by further logistic regression analysis, which revealed a positive association between event/obesity and outcome/SI (p = 0.006, OR = 1.151, 95 % CI = 1.042–1.271).

The wire type was not an independent risk factor for SI, as shown by univariate and logistic regression analyses. This means that the titanium wire is not inferior to the stainless steel wire in this context, and we can reject the null hypothesis.

4.1. SI

Although sternotomy incision for cardiac surgery is associated with excellent clinical outcomes, SI is reported in a small but significant number of patients (1%–8%) globally. The literature also suggests that this incidence is a conservative estimate as it only accounts for patients who are identified to have sternal infection or who undergo rewiring surgery based on their medical records (El-Ansary et al., 2018). The incidence rate of SI (4.3%) in our study was similar to that in comparable studies (Alhalawani & Towler, 2013; El-Ansary et al., 2018).

The sternal dehiscence/SI has an impact on surgical treatment and prognosis. It would seem that, SI differentiates between deep SWI and superficial wound infection (mechanical barrier), and it is the most commonly used endpoint in the literature to assess poststernotomy complications. Early recognition and diagnosis of sternal complications are imperative to ensure timely management, which arrests the clinical sequelae of deep infection and mediastinitis (El-Ansary et al., 2018).

To our mind, our standard technique of sternal closure—interlocking multitwisted wires—is an effective, simple, and reliable method of sternotomy closure. The use of our technique is supported by the results of a biomechanical study of median sternotomy closure techniques by Casha et al., who recommended the use of at least eight straight wires—four figure-of-eight wires or four multitwist wires. This study demonstrated that the closure device should have a safety margin that can withstand double the maximum force applied (Casha, Yang, Kay, et al., 1999).

As is commonly accepted in orthopedic surgery, we agree with Cheng et al., who assumed that more stable bony fixation leads to better healing in sternal closure. Undoubtedly, other factors, such as bacterial contamination, sternal ischemia, diabetes, and unusual disrupting forces (violent coughing) also contribute to healing problems, but many of these are beyond the control of cardiothoracic surgeons (Cheng et al., 1993).

4.2. BMI “obesity”

Overall, the most frequently described risk factor for postoperative wound healing disorders is increased body weight. One reason for this is possibly the preoperative and postoperative antibiotic dose, which is often not optimally adapted to the body weight of in patients with obesity and, thus, insufficient tissue concentration is achieved. Furthermore, deep folds of the skin may not have been adequately disinfected. Large amounts of adipose tissue may also serve as better substrates for wound infections. In addition, obesity leads to increased mechanical stress on the sternum and underlying tissue. This can lead to divergence of the wound edges or SI, thus leading to easier bacterial penetration (Milano et al., 1995). We observed a strong association between infected inframammary creases in female patients with obesity and diabetes and postoperative sternal wound infections. Based on our experience in wound clinics, we consider inframammary skin infection an important predictor and primary source of sternal infection. Attention should be paid, and eradication of such infections must be achieved before elective surgery.

Milano et al. studied 6,459 patients and concluded that obesity was the most important independent risk factor for the development of postoperative sternal complications (OR = 1.3, p = 0.0002).

In other studies, Molina et al. and Risnes et al. have shown that patients with a BMI of >30 kg/m^2 have a 2–8.9-fold increased risk of sternal complications (Molina et al., 2004; Risnes et al., 2010).

In a case-control study of 37 patients and 74 matched controls, Bitkover et al. evaluated 54 potential risk factors and concluded that obesity is one of the most important risk factors for SWI (p = 0.0033), suggesting that mechanical strain on sternotomy and SI may precede infection (Bitkover & Gårdlund, 1998).

This risk factor was also reported by Abboud et al.; obesity was an independent risk factor for surgical site infection in 9,136 patients (OR = 6.49; 95% confidence interval [CI] = 2.24–18.78) (Abboud et al., 2004b).

In our study, high BMI was the only variable among the preoperative, intraoperative, and postoperative variables that affected SI. The mean BMI of patients (n = 14/322) who developed SI in both groups was 31.7 ± 4.4 kg/m^2, while that of patient who did not develop

SI in both groups was 28.1 ± 4.6 kg/m^2 (p = 0.002). The mean BMI in the study group was 32.2 ± 5.3 kg/m^2, while that in the comparison group was 31.3 ± 3.9 kg/m^2.

4.3. Wound infection/ASEPSIS score

More than one million sternotomies are performed annually worldwide; risk factors such as diabetes, obesity, and/or osteoporosis are common and can result in complications. Deep SWI is a sternotomy complication that contributes to high mortality and morbidity despite advances in antibiotic treatment. Deep SWI contributes to 14%–47% of total mortality, with an occurrence rate of 0.5%–8%. Alhalawan et al. analyzed different sternal closure techniques in their review. Numerous innovations and efforts have been made to improve the sternal closure technique, but the ideal conditions for sternal closure have not been elucidated. An ideal procedure should consider a device that imparts suitable mechanical properties, radiopacity, biocompatibility, removability when necessary, and cost effectiveness (Alhalawani & Towler, 2013).

Different studies have implicated that suture materials increase the risk of developing SWI. Therefore, Malhotra et al. compared two conventional techniques of sternal closure (steel wire vs. polyester suture) and concluded that the use of polyester sutures for sternal closure in adult patients results in increased wound infection, wound pain, and late wound complications, but lower mediastinal drain output (Malhotra et al., 2014).

Additionally, Clauss et al. (2013) have reported that infection is a serious complication of operative therapy and can be related to implant materials. Biofilm formation can be reduced by the materials used. Titanium implants have less biofilm formation than stainless steel implants, and infections may be acute and easy to detect, but can also present as low-grade infections that are difficult to diagnose and likely to be missed (Clauss et al., 2013).

For simpler statistical analysis, we divided the patients into two groups according to a ASEPSIS cutoff score of 40—ASEPSIS score <40, mild-to-moderate wound infection or no wound infection, and ASEPSIS score >40, severe wound infection.

In our study, both suture materials led to satisfactory wound healing, as shown by a mean ASEPSIS score of <10 (2.4 ± 9.5) in both groups. The incidences of moderate and severe wound infections were comparable between the groups. The percentage of severe wound infection with an ASEPSIS score of >40 in the study and comparison groups was 3,1% and 1,9 %, respectively; it was slightly higher in the study group, but was statistically not significant (p = 0.474).

These results are similar to those reported by Jonkers et al., who included 1885 patients who underwent cardiac surgery in a prospective study. Superficial wound infection and deep SWI were diagnosed in 4.7% and 1.5% patients during hospitalization, in 6.8% and 4.6% patients at 30 days postoperatively, and in 9.0% and 7.3% patients at 90 days postoperatively (Jonkers et al., 2003). Additionally, the estimated incidence of mediastinitis (1.6%) in our study is similar to that reported in other studies (Abboud et al., 2004b; Risnes et al., 2010).

Among the patients who developed wound infection regardless of superficial wound infection or deep SWI in the stainless steel group, wound swabs were obtained from 11 patients. Wound swabs were sterile in nine patients and positive in only two patients. During the course of treatment, two patients who initially showed sterile culture developed superimposed infections on further culture. A possible explanation is that the process of wound infection in the patients was due to a subclinical reaction to the stainless steel wire (mechanical disturbance of wound healing). In the study (titanium) group, wound swabs were obtained from eight patients. Five patients showed positive culture results, while the other three did not. The most common organism was *S. aureus*.

Contrary to the findings reported in the literature regarding the well-known risk factors for SI and wound infection, such as female sex, diabetes mellitus, advanced age, COPD, smoking, peripheral vascular disease, renal insufficiency, use of BIMA graft, operation time, long ICU stay, and delirium (Abu-Omar et al., 2017), our study did not confirm the role of these variables as independent risk factors for wound infection and SI. However, owing to a relatively small sample size comparable to other studies published in the literature, caution must be exercised as the findings might not be precise.

4.4. Postoperative pain

The etiology of increased postoperative pain with stainless steel wires compared to that with titanium wires is unclear. We presume that a mild allergic response (subclinical) to stainless steel wires may lead to edema, inflammation, swelling, and subsequently pain (Ancalmo et al., 1993; Fine & Karwande, 1990; Lopez et al., 2016; Mesinkovska et al., 2012; Zywicka et al., 2019). We have noticed that an increasing number of patients in whom the sternum was closed with stainless steel wires presented to our wound clinic with pain affecting their quality of life in the absence of cachexia, infection, and wire fistula, which could support our assumptions of subtle or subclinical allergic response to nickel - wire intolerance -. Persistent sternal pain after median sternotomy for open heart surgery is a relatively common

complaint. Many poststernotomy pain syndromes have been considered to have a specific cause–effect relationship directly related to an underlying pathological process (e.g., infection, nonunion, protruding wire, and ischemia). Most cases appear to be poorly defined; however, they have been attributed to nonspecific anxiety-related or muscular pain disorders. Fine et al. reported a case of disabling chest pain after open heart surgery through a median sternotomy incision in which stainless steel sutures were used for sternal closure. Removal of sternal wires led to complete pain relief (Fine & Karwande, 1990).

Lopez et al. presented a case of a patient who developed chronic tissue overgranulation over a sternotomy wound 8 weeks postoperatively. The wires were made of standard surgical stainless steel, which is an alloy of nickel and chromium. The sternal wires were removed as they were the most likely cause of the local tissue reaction. Surgery was performed 5 months after coronary artery bypass grafting (CABG). All the sternal wires were removed. The reoperated wound healed well (Lopez et al., 2016).

In the case reported by Lopez et al., the patient had no previous metal hypersensitivity; however, he had a known allergy to penicillin and seafood and had previously developed blisters around his surgical plasters. He also had eczema, which flared up prior to surgery. However, there is limited evidence to suggest a correlation between known hypersensitivity and development of such an allergic reaction (Lopez et al., 2016).

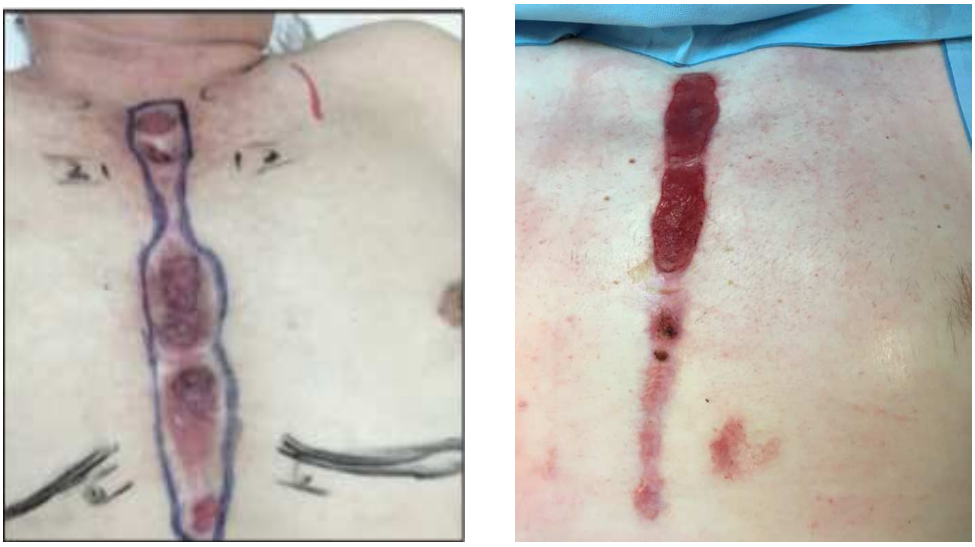

Figure 8 Right: eruptions along the sternotomy wound due to overgranulation (Lopez et al., 2016). Left: overgranulation of the wound (Image Source: Wound clinic, Heart Centre Dresden)

Additionally, persistent postoperative incisional pain after aortocoronary bypass surgery was reported by a patient in whom allergies to metals contained in the stainless steel suture used for sternal closure were confirmed by patch testing. The symptoms resolved promptly after

the sutures were removed (Ancalmo et al., 1993). Another possible explanation for the greater postoperative pain in the stainless steel group may be attributed to the increased stiffness of the stainless steel wire compared to that of the titanium wire; in other words, the stainless steel wire is harder than the titanium wire.

4.5. Type of the wire

There are no special clinical studies on the safety of titanium wires; however, many studies (Arnoni, Dantas, Arnoni, Neto, et al., 2013; Clauss et al., 2013) have been conducted on other similar surgical medical devices made of titanium. In a comparative study, Clauss et al. demonstrated that in the correction of toe deformities, titanium K wires showed superior clinical outcomes to stainless steel K wires. This appears to be attributable to the reduced infection rates. Titanium plates and screws are also used for sternal closure, and many studies have shown their safety in patients (Arnoni, Dantas, Arnoni, Nigro Neto, et al., 2013). Nickel is a common contact allergen; therefore, the potential of stainless steel to cause sensitization should be explored to reveal any possible hidden causes of postoperative wound healing disorders.

Although some surgeons have expressed skepticism that allergy to the sternal wire is a real condition, there is ample evidence in the published literature on such hypersensitivity reactions, especially in orthopedic surgery (Pacheco, 2019). A German consensus paper has suggested that titanium implants should be used in all patients with a history of metal allergies (Teo & Schalock, 2016).

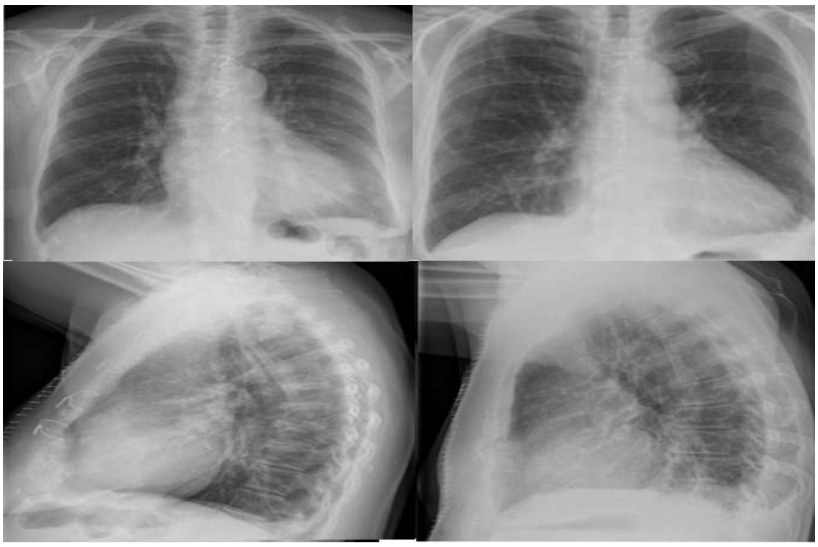

Figure 9 Chest X-rays posteroanterior and lateral views showing the difference in radio-opacity between the stainless steel (left) and titanium wires (right). (Image Source: Wound clinic, Heart Centre Dresden)

Both stainless steel and titanium wires are comparable in terms of postoperative SI, superficial wound infection, and deep SWI. Our study has confirmed that the titanium wire is safe and noninferior to the standard stainless steel wire. Therefore, the null hypothesis was refuted.

4.6. Rising potential impact of metal hypersensitivity on other specialties

4.6.1. Orthopedics implant

Metal hypersensitivity has been studied as a potential cause of complications after total joint arthroplasty, since the first case of metal-related dermatitis was reported in 1966 (Teo & Schalock, 2016).

The potential allergic complications after implantation of orthopedic metal devices include cutaneous eruptions, chronic joint pain, edema, loosening, and joint failure. Mesinkovska et al. (2012) support patch testing before surgical implant surgery in patients with a history of hypersensitivity to metals, such as those found in costume jewelry, belt buckles, or watches. In their study, nickel was found to be the most common allergen. In this study, the surgeons were cognizant of the patch test results and dermatologist recommendations when selecting implants. Titanium alloys and oxidized zirconium–niobium are the most commonly chosen allergen-free implants (Mesinkovska et al., 2012). The study confirmed the need for surgeons and dermatologists to work together and establish guidelines with the goal of identifying patients who would benefit before surgical implant in a bone or joint as a safe measure to avoid complications.

The existing literature shows conflicting results, and the degree to which metal sensitivity affects implant viability is highly contested. A large case-control study including 356 cases and 712 controls found that the risk of surgical revision of total hip arthroplasty did not increase in patients with metal allergies and that the risk of metal allergy did not increase after total hip arthroplasty (Thyssen et al., 2009). However, other studies have shown that biofilm formation can be reduced by the materials used. Titanium implants have less biofilm formation than stainless steel implants (Harris et al., 2007; Moriarty et al., 2009; Schlegel & Perren, 2006; Sheehan et al., 2004).

4.6.2. Dental implant

There are a huge range of potential metallic allergens in dental implants, orthodontic devices, and restorations, including—but not limited to—gold, mercury-containing amalgam, nitinol/nickel, titanium, and palladium. There are numerous case reports that establish a link

between dental metallic implants and allergic contact dermatitis, with early cases dating back to 1966, in which generalized dermatitis resolved completely after removal of dentures made from chromium–nickel alloy or chromium–cobalt alloy (Teo & Schalock, 2016).

In a cross-sectional observational study that included 228 participants aged 11–45 years, Zigante et al. found that the prevalence of allergic sensitization to titanium in patients undergoing orthodontic treatment was 4%, while to that to nickel 14%. Hypersensitivity to both metals at the same time was present in 2% participants (Zigante et al., 2020).

Hosoki et al. described a patient who developed allergic contact dermatitis caused by titanium screws and dental implants. They concluded that the allergic risk of titanium material is lower than that of other metallic materials. However, preimplant patients should be asked about their history of hypersensitivity reactions to metals, and patch testing should be recommended for patients who have experienced such reactions.

4.7. Limitation of the study

Given the paucity of the literature on this topic, we have intentionally decreased the eligibility criteria of this study (see exclusion criteria) to increase the internal validity and used the "decrease the noise to amplify the signal approach." Therefore, further randomized studies should be conducted to compare the use of titanium wires with that of steel wires in patients at a high risk for mediastinitis to confirm their safety and increase the external validity (generalizability) of our results.

Blinding in surgical research is not an easy task because it is very difficult to blind the surgeon, who can be a source of bias.

Regarding postoperative pain, one may argue that pain, being a clinical scale, is subject to bias (observer bias or reporting bias) due to subjectivity in symptoms assessed, but the patients and outcome assessors/ward nurses were unaware of the type of wire used. Considering that postoperative pain was the secondary endpoint in our study. Therefore, we consider these findings as exploratory findings, and another study should be recommended and designed to answer this specific question.

Although the skin patch test is the gold standard method in diagnosing contact allergy, its efficacy is debatable in cardiac surgery and is not well established in preoperative workup. Therefore, our patients were asked for a history of hypersensitivity to metals, without patch skin testing.

Considering that nickel hypersensitivity is more common in women than in men, with a ratio of 5:1, our study was not balanced in terms of sex (18.9% women vs. 81.1% men) as most of our patients underwent CABG (90.7%), and men were more affected than women. It would be interesting to know the prevalence of poststernal wiring pain in women compared to that in men.

The take home messages for surgeons is to be aware of the possibility of developing an allergic reaction to wires, especially in patients with a history of multiple allergies. This could be due to persistent unexplained postoperative chest pain or chronic nonhealing yet stable overgranulating sternotomy wound in the absence of cachexia, infection, and wire fistula. In patients with documented hypersensitivity to nickel, other alternative closure methods should preferably be considered, such as the titanium wire, which has been proven to be safe and noninferior to the stainless steel wire in our study.

4.8. Conclusion

One significant advantage of using metallic biomaterials as implant materials is their inertness. The complications associated with the use of sternal closure suture materials are mainly related to the procedure itself and include risks such as pain, hemorrhage, inflammation and infection, injury to adjacent structures, malpositioning of the suture ligature, dehiscence, or SI. However, some potential risks are associated with the suture or the suture material, such as allergic reactions due to hypersensitivity, infection, or rupture of the suture, followed by dehiscence and its consequences.

Stainless steel wires have been extensively used for decades and are well established as surgical suture materials. Titanium wires are a good alternative and have been proven to be safe and effective for sternal closure. In our study, the titanium wire was associated with lower postoperative pain than the stainless steel wire, an exploratory finding. Further randomized controlled, multicentric studies are needed to prove or refute our findings.

5. Summary

Median sternotomy, first popularized by Julian et al. in 1957, has become the most commonly used incision in cardiothoracic surgery. Although the closure of this incision is usually simple and straightforward, healing complications such as instability, nonunion, and infection occur in 0.3%–8% patients undergoing cardiac surgery. These complications increase mortality and prolong morbidity. Despite several technical variations and improvements in sternal closure over the years, a small percentage of patients experience sternal wound complications, among which deep infections involving the sternal bone and mediastinum are the most relevant.

Although many factors are known to increase the risk of SWI, some studies have shown nickel as a risk factor for SWI. Sternum closure using steel wires containing nickel is a potential risk factor due to the known allergic reactions to this material, and the number of patients with an "undiscovered" allergy is underreported.

Stainless steel wires have been extensively used for decades and are well-established as surgical suture materials. Titanium wires have only been used as an alternative to steel wires in patients with known allergy to nickel. However, there is a paucity of literature regarding the safety of using titanium wires compared to that of steel wires to close the sternum after cardiac surgery in terms of early sternal dehiscence, sternal infection, and wound pain. Therefore, this study aimed to demonstrate the noninferiority of titanium wires, even in patients without a known allergy. Additionally, the handling of titanium wires compared to that of steel wires was documented by surgeons.

We performed a single-center randomized prospective, single-blinded study at Heart Center Dresden, Technical University of Dresden, comparing the titanium wire to the standard stainless steel wire in our center.

A total of 322 patients who underwent elective cardiac surgery through median sternotomy were randomly assigned to sternal closure using either stainless steel wires (n = 161) or titanium wires (n = 161). Patient characteristics were similar in both groups.

Postoperatively, we focused on the incidence of SI as the primary endpoint, and postoperative pain and wound infection as the secondary endpoints. The follow-up period was 3 months. During follow-up, 14 patients had SI— six (3.7%) patients in the study group and eight (5%) patients in the comparison group ($p = 0.585$). Therefore, the titanium wire is comparable and not inferior to the standard stainless steel wire in terms of postoperative SI.

Our study demonstrated a statistically significant difference between the group in terms of postoperative pain according to numeric pain rating scale on the third and seventh days. Patients in the study group experienced lower postoperative pain than those in the comparison group on both days ($p = 0.032$ and $p = 0.024$, respectively). We assumed that the increased postoperative pain in the study group could be attributed to nickel intolerance or undiscovered nickel allergy or to the increased stiffness of the stainless steel wire compared to that of the titanium wire; the stainless steel wire is harder than the titanium wire.

There was no statistically significant difference between both groups in terms of postoperative wound infection. The percentage of patients who developed severe wound infection with an ASEPSIS score of >40, mediastinitis, osteomyelitis, and wound revision in the study and comparison groups was 3.1% vs. 1.9% ($p = 0.474$), 1.2% vs. 1.9% ($p = 0.652$), 1.9% vs. 2.5 ($p = 0.702$), and 5% vs. 4.3% ($p = 0.791$), respectively.

In our study, univariate analysis showed that BMI was the only independent risk factor for SI, with a mean BMI of 31.7 ± 4.4 kg/m^2 among patients with SI and 28.1 ± 4.6 kg/m^2 among those without SI ($p = 0.002$). This positive finding was confirmed by further logistic regression analysis, which revealed a positive association between event/obesity and outcome/SI ($p = 0.006$, OR = 1.151, 95 % CI = 1.042-1.271).

In our experience, the use of titanium wires has also proven to be safe and effective in sternal closure. Surgeons should be aware of the possibility of developing an allergic reaction to the wires, especially in patients with a history of multiple allergies.

6. Zusammenfassung

Die mediane Sternotomie, die erstmals 1957 von Julian und Kollegen propagiert wurde, ist heute der am häufigsten verwendete Zugangsweg in der Herz-Thorax-Chirurgie. Obwohl der Verschluss des Thorax in der Regel einfach und unkompliziert ist, treten bei 0,3% bis 8% der herzchirurgischen Patienten Wundheilungsstörungen wie Instabilität und Infektionen auf. Diese Komplikationen führen zu einer erhöhten Sterblichkeitsrate und einer erhöhten Morbidität. Trotz weiterentwickelten Verschlusstechniken leidet ein kleiner Teil der Patienten an schwerwiegenden sternalen Wundheilungsstörungen mit Beteiligung des Sternum-Knochens sowie des Mediastinums. Diese Komplikationen stellen eine relevante Prognoselimitierung dar.

Drähte aus Stahl werden seit Jahrzehnten in großem Umfang verwendet und sind als chirurgisches Nahtmaterial gut etabliert. Einige Studien haben jedoch gezeigt, dass Nickel eine Allergie getriggerte Entzündungsreaktion auslösen kann. Die routinemäßigen verwendeten nickelhaltigen Stahldrähte stellen somit einen potenziellen Risikofaktor für Wundheilungsstörungen dar.

Eine Alternative wären nickelfreie Titandrähte. Bisher wurden Titandrähte nur bei Patienten mit einer bekannten Nickelallergie verwendet. Es gibt jedoch nur wenig Literatur über die Sicherheit der Verwendung von Titandrähten im Vergleich zu Stahldrähten zum Verschluss des Sternums nach herzchirurgischen Eingriffen im Hinblick auf Sternum-Dehiszenz, Wundheilungsstörung und Wundschmerzen. Ziel dieser Studie ist es daher, die Nichtunterlegenheit von Titandrähten auch bei Patienten ohne bekannte Allergie nachzuweisen.

Am Herzzentrum Dresden der Technischen Universität Dresden wurde eine randomisierte, prospektive, einfach verblindete Studie durchgeführt, in der man den Titandraht mit dem Standarddraht verglichen hat.

322 Patienten, die sich einer elektiven Herzoperation durch mediane Sternotomie unterzogen haben, wurden nach dem Zufallsprinzip entweder einem Sternum-Verschluss mit Edelstahldrähten (n = 161) oder mit Titandrähten (n = 161) zugewiesen. Die Merkmale der Patienten waren in beiden Gruppen statistisch vergleichbar.

Postoperativ wurde die Inzidenz der Sternum-Instabilität als primären Endpunkt und auf postoperative Schmerzen und Wundheilungsstörung als sekundären Endpunkt erhoben. Die Nachbeobachtungszeit betrug 3 Monate. Während der Nachbeobachtung traten insgesamt

14 Patienten mit Sternum-Instabilität auf: 8 Patienten in der Edelstahlgruppe (5%) und 6 Patienten in der Titangruppe (3,7%) (p = 0,585). Daher ist der Titandraht in Bezug auf die postoperative Sternum-Instabilität mit dem Standard-Edelstahldraht (Nickel) vergleichbar bzw. nicht unterlegen.

Zusätzlich erbrachte diese Studie einen statistisch signifikanten Unterschied zwischen der Edelstahl- und der Titangruppe in Bezug auf die postoperativen Schmerzen gemäß der numerischen Schmerzbewertungsskala "NRS" am 3. und 7. postoperativen Tag. Die Patienten in der Titangruppe hatten weniger postoperative Schmerzen (p = 0,032 bzw. 0,024). Die vermehrten postoperativen Schmerzen in der Edelstahlgruppe könnten zum einem auf eine Nickelunverträglichkeit bzw. eine unentdeckte Nickelallergie mit entsprechenden entzündlichen Reaktionen zurückzuführen sein. Die höhere Steifigkeit des Edelstahldrahtes im Vergleich zum Titandraht mit konsekutiver vermehrter ossärer Reizung könnte zum anderen ein alternatives Erklärungsmodell sein.

Der Prozentsatz der Patienten, die eine schwere Wundinfektion mit einem ASEPSIS-Score >40 entwickelten, betrug 1,9% gegenüber 3,1% (p = 0,474), Mediastinitis 1,9% gegenüber 1,2% (p = 0,652), Osteomyelitis 2,5% gegenüber 1,9% (p = 0,702), Wundrevision 4,3% gegenüber 5% (p = 0,791) in der Edelstahl- bzw. Titan-Gruppe.

In dieser Studie zeigte die univariate Analyse, dass der BMI mit einem mittleren Wert von 31,7 ± 4,4 kg/m^2 bei Patienten mit Sternum-Instabilität und 28,1 ± 4,6 kg/m^2 bei denen ohne Sternum-Instabilität der einzige unabhängige Risikofaktor für Sternum-Instabilität war (p = 0,002). Dieses Ergebnis wird durch eine weitere logistische Regressionsanalyse bestätigt, welche einen positiven Zusammenhang zwischen Ereignis/Fettleibigkeit und Ergebnis/Sternum-Instabilität aufzeigt (p = 0,006, OR = 1,151, 95 % CI = 1,042-1,271).

Die Verwendung von Titandrähten beim Sternum-Verschluss erwies sich als sicher und wirksam. Der Chirurg sollte sich der Möglichkeit einer allergischen Reaktion auf die Drähte bewusst sein, insbesondere bei Patienten mit einer mehrfachen allergischen Vorgeschichte und entsprechend die Titandrähte als eine gute gleichwertige Alternative sehen.

7. List of figures

8. List of Tables

9. List of Abbreviations

ADL	Activities of daily living
AP	Anteroposterior
BIMA	Bilateral Internal Mammary Artery
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CD11c+	Cluster of Differentiation 11c+
CD3+	Cluster of Differentiation 3
CD4+	Cluster of Differentiation 4
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed Tomography
DM	Diabetes Mellitus
DR	Dendritic Cells
DSWIs	Deep Sternal Wound Infections
ECM	Extracellular matrix
GFR	Glomerular Filtration Rate
IMC	Intermediate Care
I.V	Intravenous
ICU	Intensive Care Unit
INF-γ	Interferons-γ
Kg	Kilogram
kPa	Kilopascal
LIMA	Left Internal Mammary Artery
MCSD	Minimal Clinical Significance Difference
MDCT	Multidetector Computed Tomography
MHC	Major Histocompatibility Complex
MMPs	Matrix metalloproteinases
MRI	Magnetic Resonance Imaging
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide
N	Newtons
N	Sample size
NRS	Numerical Pain Rating Scale
OR	Odd Ratio
p.r.n	As needed/required

PVD	Peripheral Vascular Disease
S.aureus	Staphylococcus aureus
SI	Sternal Instability
SS	Stainless steel
SSI	Surgical Site Infection
SWI	Sternal Wound Infection
Ti CP	Commercially pure Titanium
Ti-6A 4V (ELI)	Extra Low Interstitial 6% Aluminum and 4% Vandium
TiO2	Titanium Dioxide

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Anlage 1

Technische Universität Dresden Medizinische Fakultät Carl Gustav Carus
Promotionsordnung vom 24. Juli 2011

Erklärungen zur Eröffnung des Promotionsverfahrens

1. Hiermit versichere ich, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe; die aus fremden Quellen direkt oder indirekt übernommenen Gedanken sind als solche kenntlich gemacht.

1. Bei der Auswahl und Auswertung des Materials sowie bei der Herstellung des Manuskripts habe ich Unterstützungsleistungen von folgenden Personen erhalten:
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1. Weitere Personen waren an der geistigen Herstellung der vorliegenden Arbeit nicht beteiligt. Insbesondere habe ich nicht die Hilfe eines kommerziellen Promotionsberaters in Anspruch genommen. Dritte haben von mir weder unmittelbar noch mittelbar geldwerte Leistungen für Arbeiten erhalten, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen.

1. Die Arbeit wurde bisher weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde vorgelegt.

1. Die Inhalte dieser Dissertation wurden in folgender Form veröffentlicht:
……
……
……
1. Ich bestätige, dass es keine zurückliegenden erfolglosen Promotionsverfahren gab.
……

1. Ich bestätige, dass ich die Promotionsordnung der Medizinischen Fakultät der Technischen Universität Dresden anerkenne.

1. Ich habe die Zitierrichtlinien für Dissertationen an der Medizinischen Fakultät der Technischen Universität Dresden zur Kenntnis genommen und befolgt.

Ort, Datum

Unterschrift des Doktoranden

Anlage 2

Hiermit bestätige ich die Einhaltung der folgenden aktuellen gesetzlichen Vorgaben im Rahmen meiner Dissertation

das zustimmende Votum der Ethikkommission bei Klinischen Studien, epidemiologischen Untersuchungen mit Personenbezug oder Sachverhalten, die das Medizinproduktegesetz betreffen
Aktenzeichen der zuständigen Ethikkommission 287062019

die Einhaltung der Bestimmungen des Tierschutzgesetzes
Aktenzeichen der Genehmigungsbehörde zum Vorhaben/zur Mitwirkung

……..……...

die Einhaltung des Gentechnikgesetzes

Projektnummer ……..…….……..

die Einhaltung von Datenschutzbestimmungen der Medizinischen Fakultät und des Universitätsklinikums Carl Gustav Carus.

Ort, Datum

Unterschrift des Doktoranden