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HEIDI-MARI MYLLYKANGAS

Deep sternal wound infections

Prevention and treatment

DEEP STERNAL WOUND INFECTIONS -

PREVENTION AND TREATMENT

Heidi-Mari Myllykangas

DEEP STERNAL WOUND INFECTIONS

PREVENTION AND TREATMENT

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ABSTRACT

Median sternotomy is the most common incision conducted in open-heart surgery. It provides good access to the heart and other mediastinal organs. The inherent risk of deep sternal wound infection (DSWI) has been commonly defined as around 1%. DSWI has been associated with elevated mortality, morbidity, increased length of hospitalization, and higher costs. The prevention of DSWI has been an international focus of research. However, despite much effort, the incidence has remained within the same range during the recent decades. The treatment of DSWI comprises a thorough debridement, and reconstruction with multiple different types of muscle flaps as well as omentum. In addition, negative pressure wound therapy (NPWT) has become a crucal part of the treatment during the last two decades. Nonetheless, the scientific evidence of its efficacy appears unconvincing. Recently, incisional negative pressure wound therapy (iNPWT) has been investigated in the prevention of wound complications after open-heart surgery and sternal reconstructions.

We investigated if sternal wound infections after coronary artery bypass grafting (CABG) could be prevented with iNPWT. We also evaluated the role of NPWT in the treatment of DSWI as well as the role of iNPWT after pectoralis major muscle flap reconstruction. In addition, we described two less commonly used flap reconstructions in the treatment of DSWI.

We analyzed four different study materials. The first material included a prospectively collected group of 180 high-risk patients who underwent CABG with postoperative PICO™ dressing. A group of 772 high-risk patients served as historical controls. The second material consisted of 55 patients with NPWT as a first-line treatment for DSWI and 60 patients with early muscle flap reconstruction.

The third material included ten patients who had suffered from DSWI and were treated with a reconstruction technique combining a fasciocutaneous internal mammary artery perforator (IMAP) flap with a muscle sparing pectoralis major muscle flap. Finally, the fourth material consisted of 82 patients with pectoralis major muscle flap: 24 patients with preoperative NPWT and postoperative iNPWT (PICO™), 48 patients without any forms of NPWT, and ten patients with preoperative NPWT only.

In contrast to previous studies, the use of iNPWT was not beneficial in the prevention of sternal wound infections after CABG. In the treatment of DSWI, NPWT was associated with increased mortality, a longer hospitalization length, a longer stay in the intensive care unit, and more visits to the operating room. Nonetheless, the use of iNPWT after pectoralis major muscle flap in the treatment of DSWI was associated with fewer surgical complications and a shorter hospital stay.

In addition to evaluating different forms of NPWT, we described two less frequently used flap reconstructions in the treatment of DSWI. The modified IMAP flap has not been previously described. The technique is most suitable when reconstructing large defects in multimorbid and elderly patients, in whom larger reconstructions are not appropriate. Our patient series of 57 patients with split pectoralis major muscle flap is the largest published patient series describing this technique in the treatment of DSWI. In our material, a split pectoralis major muscle flap was associated with fewer wound complications compared to other forms of pectoralis major muscle flap.

National Library of Medicine Classification: WF 900, WO 185, WO 610
Medical Subject Headings: Mediastinitis; Negative-Pressure Wound Therapy; Surgical Flaps; Wound Infection; Sternotomy; Cardiac Surgical Procedures/adverse effects

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TIIVISTELMÄ

Mediaalinen sternotomia on yleisin tekniikka, jota käytetään luomaan näkyvyys sydämen pintaan avosydänleikkauksissa, kuten ohitus- ja läppäleikkauksissa. Runsas yksi prosentti näistä leikkaushaavoista tulehtuu syviä kudoksia myöten. Rintalastan syvä haavatulehdus lisää merkittävästi kuolleisuutta, kustannuksia ja sairaalahoitojakson pituutta sekä aiheuttaa merkittäviä pitkäaikaishaittoja. Haavatulehdusten ennaltaehkäisyyn keskitetyistä resursseista huolimatta niiden esiintyvyys on pysynyt samana vuosikymmenien ajan. Rintalastan syvän haavatulehduksen kirurgisena hoitona on käytetty haavan puhdistusleikkauksen jälkeen erilaisia lihaskielekkeitä sekä vatsapaitaa syntyneen kudospuutoksen korjaamiseksi. Näiden lisäksi haavan alipaineimuohoito on parin edeltävän vuosikymmenen aikana noussut tärkeäksi osaksi hoitokaaviota. Tieteellinen näyttö alipaineimuhoidon tehosta on kuitenkin rajallista. Suljetun haavan alipaineimuhoitoa on viime vuosina tutkittu haavakomplikaatioiden ennaltaehkäisyssä sekä avosydänleikkausten että rintalastan korjausleikkausten jälkeen.

Tavoitteenamme oli selvittää, voidaanko ohitusleikkauksen jälkeisiä syviä haavatulehduksia ennaltaehkäistä käyttämällä suljetun haavan alipaineimuhoitoa. Tutkimme myös avoimen haavan alipaineimuhoidon roolia syvien sternotomiahaavainfektioiden hoidossa, sekä suljetun haavan alipaineimuhoidon roolia rintakehän lihaskielekerekonstruktioiden jälkihoidossa. Lisäksi kuvasimme kaksi harvemmin käytettyä kielekevaihtoehtoa syvän sternotomiahaavainfektion jälkeisen kudospuutoksen korjaamisessa.

Väitöskirja jakaantuu neljään osatyöhön ja sisältää neljä erillistä aineistoa. Ensimmäiseen aineistoon (osatyö I) kuului 180 prospektiivisesti kerättyä korkean

riskin potilasta, joille ohitusleikkauksen jälkeen käytettiin PICO™ alipaineimusidosta. Verrokkina toimi 772 korkean riskin potilaan historiallinen aineisto. Toinen osatyö käsitti 55 potilasta, joiden syvää sternotomiahaavainfektiota hoidettiin ensi linjassa avoimen haavan alipaineimuhoidolla ja 60 potilasta, joille tehtiin varhainen kielekerekonstruktio. Kolmas osatyö käsitti kymmenen potilasta, joiden syvän sternotomiahaavainfektion hoidossa hyödynnettiin modifioitua rintakehän sisävaltimon (IMA) perforanttikielekettä yhdistettynä lihasta säästävään pectoralis major -lihaskielekkeeseen. Neljäs osatyö käsitti 82 pectoralis major -lihaskielekkeellä hoidettua potilasta, joista 24 potilaan hoidossa käytettiin sekä avoimen haavan alipaineimuhoitoa että postoperatiivista suljetun haavan alipaineimuhoitoa PICO™ laitteella, 48 potilasta hoidettiin ilman minkäänlaista alipaineimuhoitoa ja kymmenelle potilaalle käytettiin ainoastaan avoimen haavan alipaineimuhoitoa.

Vastoin aiempia tutkimustuloksia, käyttämällä suljetun haavan alipaineimuhoitoa ohitusleikkauksen jälkeen ei onnistuttu ennaltaehkäisemään haavatulehduksia. Syvän sternotomiahaavainfektion hoidossa avoimen haavan alipaineimuhoito yhdistyi aineistossamme korkeampaan kuolleisuuteen, pitempään sairaalahoitojaksoon, pitempään tehohoitojaksoon ja suurempaan määrään leikkaussalikäyntejä. Sen sijaan sternotomiahaavainfektion hoidossa käytetyn lihaskielekkeen yhteydessä suljetun haavan alipaineimuhoito vaikutti vähentävän kirurgisten komplikaatioiden määrää sekä sairaalahoidon pituutta.

Esittelemämme modifioitu IMA -perforanttikieleke on aiemmin julkaisematon tekniikka, joka soveltuu myös iäkkäille ja monisairaille potilaille laajojen kudospuutosten korjaukseen. Kuvaamamme 57 potilaan sarja halkaistun pectoralis major -lihaskielekkeen käytöstä syvän sternotomiahaavainfektion hoidossa on suurin julkaistu potilassarja kyseisen kielekkeen osalta. Tekniikka soveltuu käytettäväksi ensisijaisena rekonstruktiovaihtoehtona ja yhdistyy aineistossamme vähäisempään määrään komplikaatioita verrattuna pectoralis major -lihaskielekkeen muihin muotoihin.

Yleinen suomalainen ontologia: sydänkirurgia; rintalasta; haavanhoito; komplikaatiot; rekonstruktio

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This is dedicated to my dear children. Sofia, who at the age of five, knew that "learning is astoundingly fun" and Daniel, who now, with all the enthusiasm of a three-year-old, could not agree more. You are the world to me.

"What if I fall?
Oh, but my darling, what if you fly?"
-Erin Hanson

Kuopio, 28 August 2021
Heidi Myllykangas

LIST OF ORIGINAL PUBLICATIONS

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I Myllykangas HM, Halonen J, Husso A, Väänänen H and Berg LT. Does incisional negative pressure wound therapy prevent sternal wound infections? Thorac Cardiovasc Surg. 2021. Online ahead of print. doi: 10.1055/s-0041-1731767

II Myllykangas HM, Halonen J, Husso A and Berg LT. Negative pressure wound therapy in treatment of deep sternal wound infections – a critical appraisal. Scand Cardiovasc J. 2021. Online ahead of print. doi: 10.1080/14017431.2021.1955963

III Myllykangas HMP, Mustonen PK, Halonen JK and Berg LT. Modified internal mammary artery perforator flap in treatment of sternal wound complications. Scand Cardiovasc J. 52: 275-280, 2018. doi: 10.1080/14017431.2018.1546897

IV Myllykangas HM, Halonen J, Husso A and Berg LT. Decreasing complications of pectoralis major muscle flap reconstruction with two modalities of negative pressure wound therapy. Scand J Surg. 2021. Online ahead of print. doi: 10.1177/14574969211043330

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CONTENTS

ABBREVIATIONS

ASO	Peripheral artery disease
BIMA	Bilateral internal mammary artery
BMI	Body mass index
CABG	Coronary artery bypass grafting
CDC	Centre of Disease Control
CRP	C-reactive protein
CT	Computer tomography
DSWI	Deep sternal wound infection
HbA1c	Hemoglobin A1c
ICU	Intensive care unit
IMA	Internal mammary artery
IMAP	Internal mammary artery perforator
iNPWT	Incisional negative pressure wound therapy
LD	Latissimus dorsi
MCI	Myocardial infarction
MRSA	Methicillin resistant Staphylococcus aureus
NPWT	Negative pressure wound therapy
SSI	Surgical site infection
SIMA	Single internal mammary artery
PRP	Platelet rich plasma
UAP	Unstable angina pectoris

1 INTRODUCTION

Median sternotomy was first described by Milton in 1897 but only later reintroduced into clinical practice by Julian *et al.* in 1957. It allows a good access to the mediastinum and is therefore used to perform open heart surgery, such as coronary artery bypass grafting (CABG), valvular replacement, aortic surgery, heart transplantation, and treatment of congenital heart disease.

Complications of open-heart surgery include atrial fibrillation, kidney injury, and bleeding. Infectious complications such as myocarditis, pericarditis, endocarditis, pneumonia, clostridium difficile infection, cardiac device infection, empyema, and sepsis may also occur. In addition, sternotomy in open heart surgery carries an inherited risk of surgical site infections, with the most feared being deep sternal wound infection (DSWI), or mediastinitis.

The need for open-heart surgery has diminished during the recent years due to the introduction of endoscopic techniques and percutaneous coronary interventions. For this reason, those patients that are selected for open-heart surgery tend to have numerous comorbidities. The numbers of isolated CABG have also declined with an increasing proportion of multiple-valve surgery, combined valve and CABG surgery, and aortic procedures. These more complex procedures carry an elevated risk of postoperative infection.

Patients undergoing open heart surgery, although considered as a clean operation, have multiple factors predisposing them to infections. The cardiopulmonary bypass used in cardiac surgery may compromise humoral immunologic defenses, reduce phagocytosis, and activate white blood cells. Systemic hypothermia may induce a degradation of clotting factors and predispose patients to bleeding. The subsequent hematoma serves as a risk factor for infections. Other risk factors include the length of the operation and the required presence of several chest catheters. For these reasons, the incidence of DSWI has remained around 1% despite the many preventive protocols in use.

There are differences in infection surveillance between institutions and countries. There are some reports that are based on voluntary reporting of the infections, which capture only acute infections, or are based on national records that have varying reliabilities. It must also be recognized that some variation in morbidity and mortality may be attributable to variations in case definitions, follow-up methods, and the criteria for patients to be accepted for surgery. These are some of the factors which explain the variance in the published study results.

Although the incidence of DSWI is low, the effect on individual patients and institutions is considerable. Even with modern treatment protocols DSWI is associated with significant mortality, morbidity, an increased number of operations, prolonged hospital stays, and thus extra costs. In addition to all the measurable consequences, the emotional burden for the patient, for the family, and for the multiprofessional team treating these complications should be taken into consideration.

Over the recent decades, many methods and algorithms for the prevention and treatment of DSWI have been proposed, but only a few have found their way into daily clinical practice. Risk factors, prevention, and treatment are still actively debated. It may even seem that there are more controversies than standardized protocols. Randomized trials in the treatment of DSWI are lacking altogether.

2 REVIEW OF THE LITERATURE

2.1 DEEP STERNAL WOUND INFECTIONS (DSWI)

2.1.1 Definition

Early infections are divided into superficial and deep infections. According to the Centre of Disease Control's (CDC) definition, an early superficial infection occurs within 30 days of the operative procedure and involves only skin and subcutaneous tissue (CDC and NHSN, 2014). Deep sternal wound infection (DSWI) reaches under the sternum, involving the mediastinal structures, sternal bone, and sternal wires.

According to CDC, the diagnosis of postoperative mediastinitis requires at least one of the three criteria:

(1) an organism isolated from culture of mediastinal tissue or fluids

(2) evidence of mediastinitis seen during the operation

(3) one of the following conditions: chest pain, sternal instability, or fever (>38° C), in combination with either purulent discharge from the mediastinum or an organism isolated from the blood culture.

It should be noted that a sternal infection with the presence of bacteremia is classified as a deep infection, according to the CDC definition, even when the sternum stays closed during the whole treatment period. On another hand, as Dubert *et al.* stated, only a portion of postoperative infections needing operative treatment fulfill the CDC criteria (Dubert *et al.*, 2015). Despite this, the treatment modalities and morbidity may be very similar.

The terminology varies between different publications. The terms post-sternotomy mediastinitis and postoperative mediastinitis are used as synonyms for DSWI. Alternatively, in some studies, DSWI and mediastinitis have been considered as two different entities. In these instances, DSWI is defined according to the CDC criteria, and mediastinitis as a clinically diagnosed purulent infection in the mediastinal space.

2.1.2 Anatomical considerations

The mediastinum is the space containing the heart and pericardium, the ascending and descending aorta, aortic arch, superior and inferior vena cava, pulmonary vessels, brachiocephalic vessels, internal mammary vessels, azygos and hemiazygos veins, the trachea, the main bronchi, nerves including the vagus nerve, the esophagus, thoracic duct, thymus, lymph nodes, and adipose tissue. Bilaterally, the mediastinum is limited by the parietal pleura.

DSWI leads to a deficiency of skin and a dead space between the sternal edges and the mediastinum. This skin deficiency can be perceived even in situations when no skin has been lost, because of disruption of the sternum and the following increase in chest circumference. The widest point of sternal separation is the caudal part of the sternum, and this is the part that is also the most vulnerable to complications after treatment. The perceived dead space in the mediastinum is augmented by fibrosis and scar formation in the mediastinal organs. This prevents their movement anteriorly to fill the dead space. The obliteration of this dead space is the cornerstone of flap reconstruction in the treatment of DSWI.

2.1.3 Classification

The El Oakley classification dating from the year 1996 is the most common classification of DSWI. It is based on the onset of the infection, presence of risk factors, and attempted therapeutic trials (El Oakley and Wright, 1996).

Table 1. The El Oakley classification

Class	Description
I	Mediastinitis presenting within 2 weeks after the operation No risk factors
II	Mediastinitis presenting at 2 to 6 weeks after the operation No risk factors
IIIa	Mediastinitis type I with one or more risk factors
IIIb	Mediastinitis type II with one or more risk factors
IVa	Mediastinitis type I, II, or III after one failed therapeutic trial
IVb	Mediastinitis presenting for the first time more than 6 weeks after the operation

Jones *et al.* proposed the following classification in 1997 after ample experience on the treatment of DSWI with flap reconstructions. The aim of this classification was to clarify decision making during the treatment process (Jones *et al.*, 1997).

Table 2. Classification of DSWI according to Jones *et al.*, 1997

Class	**Depth**	**Involved structures**
1a	Superficial	Skin and subcutaneous tissue dehiscence
1b	Superficial	Exposure of sutured deep fascia
2a	Deep	Exposed bone, stable wired sternotomy
2b	Deep	Exposed bone, unstable wired sternotomy
3a	Deep	Exposed necrotic or fractured bone, unstable, exposed heart
3b	Deep	Types 2 or 3 with septicemia

In 2007, Greig *et al.* described a classification based solely on the anatomic appearance. Type A consisted defects in the upper half of the sternum, Type B defects in the lower half of the sternum and Type C defects involved the whole sternum (Greig *et al.*, 2007).

The wide choice of reconstructive options led Anger *et al.* in 2015 to specify in more detail the classification of infections. They reported not only the infection, but the anatomical extent as well, in order to better evaluate the reconstructive options (Anger *et al.*, 2015). This classification, which considers all of the important aspects in the view of reconstruction, has yet to gain a wider acceptance.

Table 3. Classification of DSWI according to Anger *et al.,* 2015

Type	Affected tissues	Anatomic location of the wound
Type I	Loss of skin and subcutaneous tissue	Partial upper Partial lower Total
Type II	Bone exposed	Partial upper Partial lower Total
Type III	Loss sternal bone or ribs	Partial upper Partial lower Total
Type IV	Exposure of the mediastinum	Partial upper Partial lower Total

2.1.4 Pathogens

Recently, coagulase-negative staphylococci, such as Staphylococcus epidermidis, have become in many centers the most prevalent bacteria causing DSWI (Friberg, 2007; Baillot *et al.*, 2010). These are common bacteria found on the sternal area (Kühme, Isaksson and Dahlin, 2007). In other centers, Staphylococcus aureus continues to be the most common pathogen (Tang *et al.*, 2004; Lo Torto *et al.*, 2020; Piwnica-Worms *et al.*, 2020). Staphylococcus aureus is commonly found in the nasal area but not on sternal skin.

In a Finnish analysis of 109 patients with mediastinitis, Staphylococcus epidermidis was the most common pathogen followed by Staphylococcus aureus. The incidence of other pathogens was low and varying (Eklund *et al.*, 2006). These same results have been presented also in other Finnish reports (Eklund, Valtonen and Werkkala, 2005; Berg and Jaakkola, 2013; Hämäläinen *et al.*, 2021).

The incidence of methicillin resistant Staphylococcus aureus (MRSA) has varied widely in different studies. There have been even reports in which MRSA was the most common pathogen causing DSWI (Wong *et al.*, 2006; Filsoufi *et al.*, 2009; Konishi *et al.*, 2019). In a Finnish patient material, MRSA was found to be extremely rare (Eklund *et al.*, 2006; Berg and Jaakkola, 2013). It is noteworthy that the mortality of DSWI caused by MRSA is higher than that caused by other pathogens (Mekontso-Dessap *et al.*, 2001; Karra *et al.*, 2006).

The incidence of candida infection has varied from zero to a value as high as 20.5% of all DSWI (Modrau, Ejlertsen and Rasmussen, 2009). Candida infections carry a higher risk of mortality and require longer treatment periods compared to infections caused by other pathogens (Modrau, Ejlertsen and Rasmussen, 2009). In a recent Finnish study an increased number of candida infections was associated with the use of NPWT (Hämäläinen *et al.*, 2021).

It is important for hospitals to be aware of the local distribution of pathogens. This knowledge should be utilized when selecting the appropriate antibiotics for preoperative prophylaxis and for first-line empiric treatment of infection (Karra *et al.*, 2006). The optimal preventive methods may also vary according to the institutional range of pathogens.

Gårdlund *et al.* suggested that there are three different types of DSWI with three different types of pathogens and pathogenesis (Gårdlund, Bitkover and Vaage, 2002). In this theory, coagulase negative staphylococci are connected to sternal dehiscence, obesity, and chronic pulmonary disease. The theory postulates that a minor skin infection could spread deeper because of the instability of the sternum. These pathogens are more rarely connected to septic infection (Class 1). DSWI by Staphylococcus aureus is less likely connected to instability of the sternum and may arise from perioperative contamination, possibly from nasal carriage (Class 2). These infections may be more severe and require a more aggressive surgical approach (Floros *et al.*, 2011). The third type of DSWI is an infection caused by gram negative rods (Class 3). The infection may spread from concomitant infections in other sites by contamination or via hematogenic spread in the postoperative period. These are more likely early onset infections with a fulminant course.

2.1.5 Incidence and risk-factors

The incidence of DSWI has recently been estimated as being around 1.25–1.6% (Sears *et al.*, 2016; Juhl *et al.*, 2017; Hirahara *et al.*, 2020). The incidence rates in Finland have been reported in a range of 1.0–1.6% (Eklund *et al.*, 2006; Berg and

Jaakkola, 2013; Hämäläinen *et al.*, 2021). It is recognized that the incidence varies between different surgical procedures. Isolated valvular surgery has been reported with the lowest rate of DSWI (1.2–1.3%). The incidence of DSWI has been estimated 1.6–1.8% for isolated CABG and 1.6–2.8% for isolated thoracic aortic surgery. A combination of operations, e.g. combined CABG and valvular surgery, elevates the rate of DSWI into 2.7–2.8% and somewhat higher to 3.0–3.4% with combined CABG and thoracic aortic surgery (Kubota *et al.*, 2013; Hirahara *et al.*, 2020).

It has been speculated that the aging of the population, the rising incidence of diabetes and obesity, and a growing number of re-do CABG increases the rate of DSWI, and other complications (Fowler *et al.*, 2005). Furthermore, as the rates of percutaneous procedures increase, patients selected for open-heart surgery may have more advanced coronary artery disease (Matros *et al.*, 2010). It seems that despite the advantages in the perioperative treatment, the incidence of DSWI has remained more or less the same during the last decades (Eklund *et al.*, 2006; Baillot *et al.*, 2010; Sears *et al.*, 2016). However, there are some reports of a decline in the incidence, to which effective treatment of diabetes has contributed significantly (Matros *et al.*, 2010).

There are large number of studies analyzing the risk factors for DSWI. Identifying and modifying risk factors is essential to effective prevention. In many studies, diabetes and obesity have been considered as the two most important risk factors, although some controversy remains. In their multivariate analysis Gelijns *et al.* did not find either of these conditions as an independent risk factor for postoperative infection, in an analysis which grouped all postoperative infections together (Gelijns *et al.*, 2014).

The most prevalent risk factors have been gathered in the tables below, with some potential known or speculated mechanisms. However, because of the vast number of publications concerning the matter, only a minor part of the studies is cited here.

In 2005, Fowler et al. described a validated model to identify those patients who have an elevated risk for major infections after cardiac surgery (Fowler *et al.*, 2005). This model has been widely used as a basis of studies evaluating different preventive methods.

Table 4. Preoperative risk factors for DSWI

Risk factor	Proposed mechanism	Authors
Obesity	Decreased perfusion Mechanical stress Less effective penetration of antibiotics	Hollenbeak *et al.*, 2000; Jakob *et al.*, 2000; Prabhakar *et al.*, 2002; Crabtree *et al.*, 2004; Cayci *et al.*, 2008; Filsoufi *et al.*, 2009; Bryan and Yarbrough, 2013; Kubota *et al.*, 2013; Lemaignen *et al.*, 2015; Balachandran *et al.*, 2016; Konishi *et al.*, 2019
Diabetes	Impaired immune system Impaired wound healing	Jakob *et al.*, 2000; Crabtree *et al.*, 2004; Tang *et al.*, 2004; Cayci *et al.*, 2008; Sachithanandan *et al.*, 2008; Filsoufi *et al.*, 2009; Bryan and Yarbrough, 2013; Kubota *et al.*, 2013; Lemaignen *et al.*, 2015; Balachandran *et al.*, 2016
Elevated HbA1c		Biancari and Giordano, 2019
Diabetes with oral medication	Difficulty to control perioperative glucose values	Floros *et al.*, 2011
Female gender	Inferolateral tension by large breasts	Crabtree *et al.*, 2004; Balachandran *et al.*, 2016
Chronic lung disease / Respiratory failure	Persistent coughing in postoperative period	Filsoufi *et al.*, 2009; Kubota *et al.*, 2013; Gelijns *et al.*, 2014; Lemaignen *et al.*, 2015
Heart failure		Tang *et al.*, 2004; Floros *et al.*, 2011; Gelijns *et al.*, 2014
Elevated creatine level / kidney failure		Hollenbeak *et al.*, 2000; Kubota *et al.*, 2013; Gelijns *et al.*, 2014
Corticosteroids	Impaired wound healing Reduced host immunity	Gelijns *et al.*, 2014

Smoking	Impaired microcirculation	Cayci *et al.*, 2008; Sachithanandan *et al.*, 2008; Sepehripour *et al.*, 2012
Previous stroke		Tang *et al.*, 2004; Cayci *et al.*, 2008
Hypoalbuminemia	Impaired wound healing	Rady, Ryan and Starr, 1997; Engelman *et al.*, 1999
Nasal carriage of staphylococcus	Intraoperative contamination	Jakob *et al.*, 2000; Muñoz *et al.*, 2008
Age	Decelerated wound healing	Tang *et al.*, 2004; Sachithanandan *et al.*, 2008; Lemaignen *et al.*, 2015
ASO	Reduced perfusion	De Paulis *et al.*, 2005
Connective tissue disorder		Hollenbeak *et al.*, 2000
MRSA	Intraoperative contamination	Mekontso-Dessap *et al.*, 2001
Previous myocardial infarction		Filsoufi *et al.*, 2009
Cardiogenic shock		Kubota *et al.*, 2013

Table 5. Peri- and postoperative risk factors for DSWI

Risk factor	Proposed mechanism	Authors
Prolonged operation time	Perioperative contamination Advanced disease Technically difficult operation Increased blood loss	Filsoufi *et al.*, 2009; Gelijns *et al.*, 2014; Konishi *et al.*, 2019
Blood transfusions	Suppression of immune system Effect is dose dependent	Crabtree *et al.*, 2004; Floros *et al.*, 2011; Gelijns *et al.*, 2014; Lemaignen *et al.*, 2015; Balachandran *et al.*, 2016
Hyperglycemic episode		Gelijns *et al.*, 2014
Prolonged intubation / ventilation		Sachithanandan *et al.*, 2008; Gelijns *et al.*, 2014; Lemaignen *et al.*, 2015
BIMA harvesting	Impaired circulation in the sternal area Especially in female patients?	Crabtree *et al.*, 2004; Balachandran *et al.*, 2016; Lemaignen *et al.*, 2018
BIMA, pedicled		De Paulis *et al.*, 2005
Re-operation for bleeding	Contamination Tissue ischemia and injury	Hollenbeak *et al.*, 2000; Crabtree *et al.*, 2004; De Paulis *et al.*, 2005; Filsoufi *et al.*, 2009; Balachandran *et al.*, 2016
Urgency of operation		Cayci *et al.*, 2008
Sternum left open	Contamination	Gelijns *et al.*, 2014

Use of intra-aortic balloon pump		Floros *et al.*, 2011
Previous open-heart surgery		Floros *et al.*, 2011; Kubota *et al.*, 2013
Prolonged preoperative hospital stay	Contamination	Filsoufi *et al.*, 2009
Three vessel disease		Kubota *et al.*, 2013
Postoperative vasopressin support		Kubota *et al.*, 2013; Lemaignen *et al.*, 2015

2.1.6 Mortality and costs

The mortality associated with DSWI has been estimated to vary between 0–28% (Braxton *et al.*, 2004; Eklund *et al.*, 2006; Karra *et al.*, 2006; Berg and Jaakkola, 2013; Sears *et al.*, 2016; Juhl *et al.*, 2017; Schiraldi *et al.*, 2019). The mortality rates described in a vast number of studies represent a heterogenic group of patients with different treatment protocols, and are presented in many ways, including all-cause, diagnosis-specific, in-hospital, 30-days, 90-days, and 1-year mortality.

In-hospital mortality rates have been determined to lie in a range of 1.1–19% (Goh, 2017; Schiraldi *et al.*, 2019). The mortality in the early phase is commonly caused by uncontrolled infection, sepsis, and multi organ failure (Landes *et al.*, 2007).

For practical reasons, there are fewer reports concerning the late deaths with more conflicting findings. In an English prospective cohort study, Karra *et al.* reported 19.7% 90-days mortality and 28% one-year mortality after DSWI, when counting from the original open-heart surgery (Karra *et al.*, 2006). Ten years later, Sears *et al.* found better results in the USA (Sears *et al.*, 2016). In their report 1-year mortality was 10.7%, which is still a four-fold increase compared to mortality without DSWI. Decreased survival rates after three and five years have been reported (Filsoufi *et al.*, 2009). Mortality remained double in a long-term analysis up to ten years (Braxton *et al.*, 2000).

Interestingly, the results concerning increased mortality are not uniform. A propensity score analysis conducted by Cayci *et al.* did not find any connection between DSWI and increased late mortality (Cayci *et al.*, 2008). Similarly, after adjusting for risk factors, the incidence of DSWI was not a significant independent predictor of in-hospital or late mortality in a propensity score analysis performed by Sachithanandan *et al.* (Sachithanandan *et al.*, 2008).

In a multivariate analysis, the most important independent risk factor for mortality was a longer than three-day delay from debridement to wound closure. A longer delay was associated with a more than six-fold increase in the mortality (Karra *et al.*, 2006). Other considered risk factors for mortality were age over 65 years, high serum creatinine level before the debridement, MRSA, and treatment in the intensive care unit (ICU) before the debridement (Karra *et al.*, 2006; Morisaki *et al.*, 2011).

The use of flap reconstruction has been connected with better survival (Karra *et al.*, 2006; Morisaki *et al.*, 2016). The use of NPWT has also been associated with less mortality. This topic is discussed later. It has been claimed that prompt initiation of culture-specific antibiotics within seven days of debridement significantly decreases the mortality (Karra *et al.*, 2006).

The European System for Cardiac Operative Risks Evaluation (EuroSCORE) is a well-known risk model predicting mortality after cardiac surgery. It considers several patient and operation related risk factors. The evaluation system was calibrated in 2012 since the mortality after CABG declined despite the aging population. This new version of the scoring system is called EuroSCORE II (Nashef *et al.*, 2012).

A German case-control study dating from 2010 performed by Graf *and al.* found the costs of DSWI to be almost three-fold compared to standard CABG without infections (Graf *et al.*, 2010). The additional cost was estimated to be 22 906 euros. Most of the extra costs were due to the prolonged duration of hospitalization, prolonged stay in the intensive care unit, and additional operations. The use of NPWT and the need to administer antibiotics also added to the costs. Indirect costs, or costs originating from subsequent readmissions and controls were not included in the analysis.

A similar increase in costs (2.5-fold) has been demonstrated from the USA in two significantly larger population-based studies (Speir *et al.*, 2009; Sears *et al.*, 2016). Additional costs during the first year were estimated to be around 20 000 dollars in another case-control study from the USA (Hollenbeak *et al.*, 2000).

The duration of hospitalization has been estimated to be around three to five-fold longer in patients with DSWI compared to those without infection, indisputably contributing to the additional costs (Speir *et al.*, 2009; Sears *et al.*, 2016).

2.1.7 Diagnosis

The symptoms of DSWI include purulent discharge, fever, wound dehiscence, redness, swelling, tenderness, and instability of the chest, as well as slow recovery from the original operation (Landes *et al.*, 2007; Kaye *et al.*, 2010). Sternal nonunion may be diagnosed with a positive sternal click. Signs of sepsis, such as tachycardia and hypotension, may be present. The general condition of the patient varies from stable to critically ill.

The diagnosis of DSWI is clinical. Most often DSWI is diagnosed only after initial discharge (Kaye *et al.*, 2010). Diagnosis may be supported by performing a contrast-enhanced computed tomography (CT) –scan, which may be useful also in timing and guiding surgical interventions. In CT –scan, sternal diastasis, sternal fractures, and mediastinal collections may be seen (Landes *et al.*, 2007). The presence of free gas, pleural effusions, and brachiocephalic lymph node size have been reported to be associated with DSWI (Foldyna *et al.*, 2019).

In a recent study, 18F-fluorodeoxyglucose positron emission tomography / computed tomography (18F-FDG PET/CT) was found to be superior compared to standard CT –scan in guiding debridement with fewer relapses and shorter hospital stay (Liu *et al.*, 2020). Later, diagnosis can be confirmed with positive culture samples.

2.2 PREVENTION

Many different procedures have been studied and proposed to prevent DSWI (Bryan and Yarbrough, 2013; Lazar *et al.*, 2016; Hui Yi Phoon and Chih Hwang, 2020). There has been an increasing international demand for research concerning the prevention of DSWI since in the USA the Medicare has deemed DSWI as a non-reimbursable “never” event.

In their Consensus statement issued in 2017, the European Association for Cardio-Thoracic surgery recommended the following practices to prevent surgical site infections (SSI) after open-heart surgery: prophylactic intravenous antibiotics, topical mupirocin, a shower or bath using soap, either on the day before or on the day of the surgery, continuous intravenous insulin-infusion, and skeletonized internal mammary artery (IMA) dissection if the patient has diabetes or a bilateral IMA harvest (Abu-Omar *et al.*, 2017).

In 2018, Vos *et al.* performed a literature search including 48 randomized controlled trials (Vos, Van Putte and Kloppenburg, 2018). According to their analysis, the following methods were considered as beneficial in the prevention of DSWI: antibiotic prophylaxis with a first-generation cephalosporin for at least 24 hours, application of local gentamicin before chest closure, sternal closure with (interlocking) figure-of-eight steel wires, and postoperative chest support using a corset or a vest. The authors also discussed the inevitable discrepancy between the study evidence and clinical practice. As can be noticed, these results differ somewhat from the recommendations issued only a year before.

Multiple authors have described preventive programs with multimodal preventive measures, including but not restricted to, preoperative antibiotic protocols, shaving and washing techniques, changing gloves, and appropriate postoperative dressings, with good results (Graf *et al.*, 2009; Kieser *et al.*, 2014; Konishi *et al.*, 2019). Macedo *et al.* described a decrease in the incidence of DSWI to as low as 0.095% by implementing a protocol including a chlorhexidine bath, nasal mupirocin, and oral chlorhexidine preoperatively, additional glycopeptide antibiotic prophylaxis for certain patient groups, and strict glucose control perioperatively (Macedo *et al.*, 2019).

Other methods proposed to prevent infections, in addition to those mentioned before and the ones to be discussed in the following paragraphs, include aseptic technique, effective ventilation and limiting traffic flow in the operating room, effective hemostasis, prevention of hypothermia, careful tissue handling, avoiding excess use of diathermia, careful and atraumatic sternotomy, avoidance of dead space, early extubating and removal of catheters, smoking cessation, correction of preoperative hypoalbuminemia, and management of remote infections (Bryan and Yarbrough, 2013; Lazar *et al.*, 2016).

2.2.1 Systemic and local antibiotics

Intravenous antibiotics are an established part of infection prophylaxis. Their ability to reduce postoperative infections has been consistently proved and thus proper antibiotic prophylaxis is recommended for all patients undergoing cardiac surgery (Class I, Level of Evidence A) (Abu-Omar *et al.*, 2017). However, some details concerning the choice of antibiotic, dosage, duration, and timing of prophylaxis are still debated.

The Society of Thoracic Surgeons Practice Guideline from the year 2007 recommended the administration of a first-generation cephalosporin as a first-line antibiotic prophylaxis. In an institution with high incidence of MRSA, a combination of one or two dosage of vancomycin was recommended. In a patient group with an allergy to beta-lactams, vancomycin was recommended. Vancomycin may be combined with aminoglycosides to enhance coverage toward gram negative pathogens (Engelman *et al.*, 2007). A meta-analysis by Saleh *et al.* confirmed the superiority of beta-lactams compared to glycopeptides (including vancomycin) in preventing deep and superficial sternal infection (Saleh *et al.*, 2015).

The Society of Thoracic Surgeons practice guidelines recommended administration of beta-lactams within 60 minutes from incision and completion of vancomycin infusion within one hour of incision (Abu-Omar *et al.*, 2017). However, it seems that harvesting IMA, even if harvested in a skeletonized manner, can affect antibiotic penetration into pre-sternal tissue. This was studied using microdialysis measurements from subcutaneous tissue after a considerably high dosage of Cefazolin (4g + 2g). Based on the results from that study, the writers proposed the early administration of antibiotics at least 60 minutes before incision to assure the presence of sufficient concentrations at the beginning of the operation (Andreas *et al.*, 2013).

The Society of Thoracic Surgeons Practice Guideline recommended to continue the prophylactic antibiotic treatment up to 48 hours (Abu-Omar *et al.*, 2017). This was considered as the shortest duration required to effectively prevent postoperative infection. A longer use of antibiotics was associated with increased costs, the prospect of drug toxicity, and, most importantly, the possibility of creating resistant bacterial strains, with no extra benefits (Edwards *et al.*, 2006). In a large prospective cohort study performed by Gelijns *et al.*, the use of antibiotics for longer than 48 hours seemed to increase the rate of major postoperative infections, especially clostridium difficile enterocolitis (Gelijns *et al.*, 2014).

The prospect of administrating a continuous intraoperative cephalosporin infusion was studied in a relatively large propensity score matched analysis, but no benefit in terms of decreasing deep or superficial infection rates compared to intermittent dosage was found (Magruder *et al.*, 2015). However, re-dosing of cephalosporins after four hours has been recommended and may decrease infections, at least with operations lasting more than 6.5 to 7 hours (Zanetti, Giardina and Platt, 2001).

Topical antibiotics have been also used and studied in attempts to combat DSWI. Their putative main advantage is that they can achieve very high local concentrations while maintaining low serum levels. In this way systemic adverse effects, such as nephrotoxicity and acquired bacterial resistance to antibiotics, can be avoided.

Preliminary Finnish results concerning the use of a gentamicin-collagen sponge in preventing DSWI described promising results (Eklund, Valtonen and Werkkala, 2005). These results were confirmed in a large, randomized, double-blinded Swedish study, although a significant decrease in DSWI was seen only in a subgroup of high-risk patients with diabetes or obesity (Friberg, 2007). Later, a large randomized multicentral study in the USA with high-risk patients did not detect the same benefits (Bennett-Guerrero *et al.*, 2010). In a German randomized study, a positive trend was seen but with no statistically significant evidence (Schimmer *et al.*, 2017).

Because of these conflicting results, a meta-analysis was carried out including the before mentioned randomized trials and observational studies as well. A benefit of decreasing both superficial and deep infections was seen. However, there was no effect on mortality and the positive effects were hindered in patients with bilateral internal mammary artery (BIMA) grafting (Kowalewski *et al.*, 2015).

Some promising results have been presented also concerning the use of a topical antibiotic spray (Osawa *et al.*, 2016) and topical vancomycin, applied as a slurry to the sternal edges to prevent infections (Lazar *et al.*, 2014).

2.2.2 Perioperative glycemic control

It is believed that inappropriate glycemic control preoperatively, perioperatively, and immediately after surgery increase perioperative mortality and morbidity (Lazar *et al.*, 2016). Perioperative hyperglycemia has also been associated with an elevated risk of infection (Gelijns *et al.*, 2014).

Ogawa *et al.* studied the difference in continuous insulin infusion therapy and an insulin sliding scale therapy in diabetic patients who underwent CABG with BIMA grafting. They found a significant decrease in infection rates with continuous infusion. However, the exceptionally high infection rate in the control group (1.1% versus 7.1%) hindered the valid interpretation of the results (Ogawa *et al.*, 2016).

Furnary *et al.* showed that continuous intravenous insulin infusion aimed at maintaining the serum glucose concentration between 150 and 200 mg/dL was useful in reducing perioperative mortality and DSWI (Furnary *et al.*, 1999). The beneficial effect of tight glycemic control (between 120 and 180 mg/dL) was also indicated by Lazar *et al.*, although the infections were grouped together and the number of DSWI was not mentioned in that report (Lazar *et al.*, 2004). Many other studies concerning this topic with similar results have been published (Lazar *et al.*, 2009).

Elevated levels of hemoglobin A1c (HbA1c) have been associated with an increased infection rate, which highlights the importance of maintaining optimal blood glucose levels also in the long-term before the operation (Biancari and Giordano, 2019).

In an Australian study conducted by Floros *et al.,* the increased risk of infection was notable especially in patients with type 2 diabetes. This was explained with a theory that strict glycemic control is more difficult to achieve in patients treated with oral medications (Floros *et al.*, 2011).

The Society of Thoracic Surgeons Practice Guideline recommended a continuous insulin infusion during the operation and 24 hours postoperatively for all diabetic patients (Lazar *et al.*, 2009).

2.2.3 Nasal decontamination

Jakob *et al.* demonstrated that the Staphylococcus aureus strain causing DSWI had most likely originated from the patient's own nose via endogenous route (Jakob *et al.*, 2000). Routine screening for Staphylococcus aureus nasal carriage and nasal decontamination is controversial. The European Association for Cardio-Thoracic surgery expert consensus recommended this practice. The Society of Thoracic Surgeons practice guidelines propose routine five days' mupirocin nasal administration for all patients if negative testing for staphylococcal colonization is not evident (Class I, Level of Evidence A). Screening for nasal carriage of staphylococcus was recommended prior to or at the time of admission (Abu-Omar *et al.*, 2017).

However, a randomized controlled double-blinded study by Konvalinka *et al.* failed to show any benefit of using mupirocin to prevent DSWI (Konvalinka, Errett and Fong, 2006). Similar results were reported by Gelijnst *et al.* (Gelijns *et al.*, 2014). Concerns about the extensive use of mupirocin include the risk of widespread antibiotic resistance. The costs of this protocol, although worth considering, seemed to remain relatively low (Cimochowski *et al.*, 2001).

In a relatively large study performed by Lemaignen *et al.,* universal nasal decolonization was effective in decreasing the risk of wound infections caused by Staphylococcus aureus but showed no effect in decreasing the total rate of mediastinitis (Lemaignen *et al.*, 2018).

2.2.4 Skeletonized internal mammary artery (IMA) harvesting

IMA vessels are frequently harvested for grafts because of their longevity. Harvesting two IMA vessels (BIMA harvesting) may be beneficial for long-term survival (Shi *et al.*, 2015), but may carry a risk of an increased infection rate (De Paulis *et al.*, 2005; Urso *et al.*, 2019). This is a consequence of diminished peristernal blood flow, which may inhibit healing and decrease antibiotic penetration in the area (Petzina *et al.*, 2006).

Skeletonized IMA harvesting is more time consuming and technically demanding, but preserves collaterals and the retrosternal circulation as well as internal mammary venous flow better than pedicled harvesting (Kamiya *et al.*, 2008). This could be beneficial in order to prevent DSWI (De Paulis *et al.*, 2005; Zhou *et al.*, 2019). It has been shown that harvesting IMA with the skeletonized technique may decrease the infection rates in BIMA harvesting almost to the level of a single internal mammary artery (SIMA) harvest (Tang *et al.*, 2004; Toumpoulis, Theakos and Dunning, 2007; Dai *et al.*, 2013; Zhou *et al.*, 2019; Ji *et al.*, 2020). Skeletonized dissection of the BIMA harvest has therefore been recommended (Toumpoulis, Theakos and Dunning, 2007; Abu-Omar *et al.*, 2017; Zhou *et al.*, 2019). However, the benefits have not been proved in all studies (Nishi *et al.*, 2011). Disadvantages include potentially an increased risk for graft conduit damage during harvesting.

The use of BIMA grafting in risk groups is more controversial. In their study Kurlansky *et al.* described increased survival with BIMA grafting in an elderly patient group (Kurlansky *et al.*, 2015). There was no difference in DSWI incidence between BIMA and SIMA grafts. However, De Paulis *et al.* recommended avoiding BIMA harvesting in patients with multiple risk factors (De Paulis *et al.*, 2005). Kieser *et al.* recommended avoiding BIMA grafting in obese, diabetic female patients (Kieser *et al.*, 2014). However, in a recent meta-analysis Zhou *et al.* considered the technique of skeletonized BIMA harvesting effective also in diabetic patients (Zhou *et al.*, 2019). In that study, no significant increase in infection levels was noted, in fact, BIMA grafting was associated with better long-time survival. Despite the positive results in most of the studies, the use of BIMA grafts is still limited.

2.2.5 Stable sternal closure

There are several studies investigating the possibilities to prevent infection with a more stable sternal closure. It has been speculated that there is a connection between sternal dehiscence and sternal infections. These conditions seem to share common risk factors (Fu *et al.*, 2015). From this perspective, preventing dehiscence could also prevent infections.

In a relatively small case-control study, Song *et al.* postulated that sternal plating, instead of wire-cerclage fixation, would be beneficial in high-risk patient group in the prevention of infections (Song *et al.*, 2004). Similar retrospective study design yielded different results with no benefits of plate fixation (Tugulan *et al.*, 2020). A meta-analysis conducted by Tam *et al.* concluded that there was no difference in early complications between sternal plating and wire cerclage closure (Tam *et al.*, 2018). However, a subgroup of patients with a very high risk of infection (three or more risk factors) may benefit from plating. The evidence, however, is derived from observational rather than randomized studies. The disadvantages of plating include the complication risk associated with drilling of the sternum, more difficult re-entry into the mediastinum in case of emergency, and increased costs (Nenna *et al.*, 2019).

Performing a reinforced osteosynthesis according to the Robicsek technique (Robicsek, Daugherty and Cook, 1977), did not offer any benefit in avoiding superficial or deep sternal infections in a large randomized multicenter trial (Schimmer *et al.*, 2008). Cable closure, although associated with less dehiscence, did not seem to decrease the infection rate in a meta-analysis performed by Fremes *et al.* (Fremes *et al.*, 2020). A figure of eight stabilization did not provide any additional benefit either, compared to standard wire closure in a best evidence topic (Khasati, Sivaprakasam and Dunning, 2004).

However, in a large, randomized study conducted by Bottio *et al.,* peri-sternal double crisscross wire closure was assessed as superior to a standard transsternal closure. More stable closure and prevention of both infections and dehiscence were accomplished (Bottio *et al.*, 2003).

In addition to the above-mentioned closure methods, there have also been commercial titanium closure devices introduced in order to distribute the tension over the entire length of sternotomy (Levin *et al.*, 2010). In a very recent retrospective study, the use of an external corset in female patients with large breasts was associated with a decreased infection rate (Selten *et al.*, 2021). The purpose of the corset was to reduce mechanical stress to the wound during the early ambulatory phase.

In a recent review article, Nenna *et al.* devised an algorithm with a tailored approach. The algorithm proposed single wire as a standard closure, and a figure-of-eight fixation for osteoporotic patients with zero to one risk factors. In contrast, the weave technique, sternal plates, sternal bands, or polymer cable ties, according to availability, were recommended for patients with two or more risk factors (Nenna *et al.*, 2019). However, the authors concluded that considering the advantages and disadvantages of each closure technique, it is difficult to make clear recommendations, and the experience of the surgeon plays a significant role in making the decisions.

2.2.6 Incisional negative pressure wound therapy (iNPWT)

Incisional negative pressure wound therapy (iNPWT) has been used to alter the biomechanical and physiological properties of wound healing to facilitate faster skin closure. There are several reports indicating that iNPWT normalizes the stress distribution around the incision and decreases the lateral tension (Wilkes *et al.*, 2012; Dohmen, Misfeld, *et al.*, 2014; Loveluck *et al.*, 2016). This may decrease the risk of dehiscence and a subsequent infection. An enhanced cosmetic appearance is a secondary benefit (Dohmen, Misfeld, *et al.*, 2014). The negative pressure also induced angiogenesis (Shah *et al.*, 2019). Other considered effects include reduced edema, stimulated perfusion, and protection from external infectious sources. The use of iNPWT could also help to eliminate dead space, remove exudate and blood, as well as prevent the formation of subcutaneous seromas and hematomas (Scalise *et al.*, 2016).

Two commercially available systems have been used to decrease the rate of DSWI. Both are single-use battery-powered devices applied over a closed incision. iNPWT is usually continued for five to seven days, although variation exists.

A foam-based device with a canister, Prevena™ (KCI, San Antonio, TX, USA), applies a continuous pressure of -125mmHg. A canister-free device using multilayer dressing technology, PICO™ (Smith & Nephew Ltd, Hull, United Kingdom), was introduced to facilitate the wide-spread use of iNPWT with a more economical, lightweight, and easy-to-use device. The use of the device has been well tolerated with good patient compliance (Hudson *et al.*, 2015). The device has a pre-set pressure of −80 mmHg. The PICO™ dressing manages exudate mostly through evaporative loss and does not require a canister (Malmsjö, Huddleston and Martin, 2014).

In addition, other systems, including some modified from the NPWT devices meant for open wounds, have been used in clinical practice and in some study designs (Atkins *et al.*, 2009).

Several meta-analyses and systematic reviews have been conducted to analyze the effect of iNPWT. Positive results have been reported concerning the decreased infection rate in orthopedic wounds, laparotomy wounds, caesarian section wounds, and vascular surgery (Ingargiola, Daniali and Lee, 2013; Karlakki *et al.*, 2013; Semsarzadeh *et al.*, 2015; De Vries *et al.*, 2016; Scalise *et al.*, 2016; Sahebally *et al.*, 2018; Yu *et al.*, 2018; Svensson-Björk *et al.*, 2019; Kim and Lee, 2020; Zwanenburg *et al.*, 2020). iNPWT seemed to be able to decrease the infection rate in both clean and contaminated wounds (De Vries *et al.*, 2016). The first meta-analysis including only studies with PICO™ presented positive results as well (Strugala and Martin, 2017).

It appears that iNPWT is also beneficial in preventing DSWI (Atkins *et al.*, 2009; Colli, 2011; Grauhan *et al.*, 2013, 2014; Dohmen, Markou, *et al.*, 2014; Witt-Majchrzak, Zelazny and Snarska, 2015; Jennings *et al.*, 2016; Suelo-Calanao *et al.*, 2020; Tabley *et al.*, 2020). The studies concerning this topic are summarized in Table 6. Most of the studies are non-randomized, and the smaller ones lack a control group. In these instances, an estimation of expected number of infections based on the Fowler score has been used as a substitute. As a deviation from other positive results, Ruggieri *et al.*, who included only patients with BIMA grafting, concluded that the routine use of iNPWT may not significantly reduce the risk of infections (Ruggieri *et al.*, 2019).

Conclusion from a consensus meeting (2011) recommended the use of iNPWT to be considered with all high- or at-risk patients (Segers, 2014) during that time, the evidence was limited.

Table 6. Studies published concerning iNPWT in prevention of sternal infections

Authors	**Device**	**Duration**	**Study group / DSWI**	**Control group / DSWI**	**Involvement of industry**
Atkins *et al.*, 2009	VAC™	4	57 / 0	Fowler	NR
Colli, 2011	Prevena™	5	10 / 0	Fowler	Yes
Grauhan *et al.*, 2013	Prevena™	6-7	75 / 1	75 / NR	No
Grauhan *et al.*, 2014	Prevena™	6-7	237 / NR	3508 / NR	Yes
Witt-Majchrzak, Zelazny and Snarska, 2015	PICO™	-	40 / 0	40 / 0	-
Jennings *et al.*, 2016	Prevena™	7	61 / 1	Fowler	No
Ruggieri *et al.*, 2019	-	-	161/9	266/27	-
Suelo-Calanao *et al.*, 2020	Prevena™	5	158 / 0	162 / 4	NR
Tabley *et al.*, 2020	PICO™	-	142 / 5	91 / 10	Yes

NR: not reported
Fowler: Fowler score used instead of a control group

The largest studies concerning iNPWT have been carried out in Germany by Grauham *et al*. First, a study with an obese study population undergoing median sternotomy incision was divided into groups of 75 patients each. The infection rate was significantly decreased with the use of iNPWT (Prevena™). However, even though with high-risk obese patients, the rate of infections requiring operative treatment in the control group (16%) was profound (Grauhan *et al.*, 2013). A second study analyzed the use of iNPWT in all patients with median sternotomy incision in comparison to a historical control group. Infection rates were 1.3% and 3.4%, respectively, with statistical difference but deep infections were not analyzed separately. The device manufacturer was involved in this study (Grauhan *et al.*, 2014).

Another rather large study was published in 2020 by Suelo-Calanao *et al*. They analyzed retrospectively 158 patients with iNPWT (Prevena™) and 162 patients with conventional wound dressing. Only high-risk patients with two or more risk factors were included. There were fewer infections in the iNPWT group. However, the patients in the iNPWT group were operated later and a decline in the overall incidence of DSWI with time was described as well (Suelo-Calanao *et al.*, 2020).

Two studies concerning the use of PICO™ have been published. In 2015, Witt-Majchrzak *et al.* conducted a randomized study including 40 patients in each group and detected a statistically significant decline in superficial infection rates. However, no DSWI were diagnosed (Witt-Majchrzak, Zelazny and Snarska, 2015). Later, a manufacturer funded cost-effectiveness analysis was published based on this small study (Nherera *et al.*, 2018). Very recently, a larger study with 142 patients in the study group presented significantly decreased infection rates with the use of PICO™. However, once again, the rate of DSWI in the control group (11%) was markedly high. The device manufacturer was involved in this study as well.

2.2.7 Other considered preventive methods

Activated platelets in platelet rich plasma (PRP) have been used to promote wound healing because of their capability to excrete growth factors, attract stem cells, stimulate vascular proliferation, and contain anti-microbial properties.

PRP applied topically, or inside the sternotomy wound, has been shown to reduce the rate of DSWI (Serraino *et al.*, 2015; Patel *et al.*, 2016; Kirmani *et al.*, 2017). The numbers needed to treat varied between 71−140 (Patel *et al.*, 2016; Kirmani *et al.*, 2017). It has to be recalled that the cost of PRP is relatively high and although several cost analyses have been performed, the results have been varying (Serraino *et al.*, 2015; Patel *et al.*, 2016; Kirmani *et al.*, 2017). A recent study of Vermeer *et al.* included only high-risk patients with diabetes and obesity. In their analysis, one avoided case of a deep sternal wound complication would save between 3,875−3,630 euros (Vermeer *et al.*, 2019). It is noteworthy that this study considered a deep sternal wound complication, including dehiscence, as an endpoint. The numbers of DSWI were not mentioned. However, the uncertain cost-effectiveness of the use of PRP has prevented its wider spreading.

There are several reports indicating a decrease in sternal wound infections in high-risk patients with the use of cyanoacrylate glue in sternal wound closure (Chambers and Scarci, 2010; Schimmer *et al.*, 2017). In their Best evidence -article concerning the subject, Chambers *et al.* still considered sternal wiring and multilayer suturing as the first-line method for sternotomy wound closure (Chambers and Scarci, 2010).

In the prospective randomized controlled study of Karabay *et al.*, intracutaneous suturing was associated with a higher number of superficial wound infections compared to standard transcutaneous sutures, especially in patients with diabetes (Karabay *et al.*, 2005). Triclosan-coated sutures have been investigated but not proved to be effective in preventing DSWI. Interestingly, these sutures have proven effective in preventing vein harvesting site infections in the same patient cohort undergoing CABG (Steingrimsson *et al.*, 2015).

The use of bone wax and its connection to DSWI is controversial (Bhatti and Dunning, 2003), although the importance of meticulous hemostasis is obvious. Bone wax is a nonbiodegradable material. It may inhibit bone healing and act as a foreign material inducing bacterial growth.

The use of antimicrobial skin sealant in cardiac surgery may be effective in preventing infections (Dohmen *et al.*, 2009). The application of silver-impregnated dressing on the sternotomy wound after surgery did not decrease the infection rate (Raman *et al.*, 2018). Even the use of prophylactic flap for high-risk patients has been proposed, but with no specific results to present (Kaye *et al.*, 2010).

2.3 TREATMENT

The treatment of DSWI has evolved considerably during the last decades (Singh, Anderson and Harper, 2011). Major improvements have been reported both in the survival and morbidity. The treatment comprises a meticulous debridement of devitalized and infected tissue, removal of affected sternal wires, and administration of culture-specific antibiotics. Closure of the wound can be achieved in many ways (Gudbjartsson *et al.*, 2016). The most straight-forward method is re-fixation of the sternum, and direct skin closure. With NPWT, the wound can be left to granulate and heal by secondary intention. A delayed primary closure is used in combination with conventional wound care or NPWT. Flap reconstruction with multiple different muscle, musculocutaneous, and fasciocutaneous flaps as well as omentum, can be used alone or in combination with NPWT and/or re-fixation of the sternum (Singh, Anderson and Harper, 2011; Kaul, 2017).

However, the treatment strategy, timing, and reconstructive technique are all without uniform consensus (Sjögren *et al.*, 2006; Juhl, Koudahl and Damsgaard, 2012; Rupprecht and Schmid, 2013; Cotogni, 2015; Goh, 2017; Kaul, 2017; Hui Yi

Phoon and Chih Hwang, 2020). Multiple algorithms have been proposed to standardize the treatment, but none has gained international acceptance.

The treatment of DSWI is divided between cardiothoracic and plastic surgeons. There are considerably differences in practices of referral in different institutions and countries. The matter of patient distribution between the two disciplines has seldom been directly addressed. The importance of multidisciplinary teamwork is often emphasized by plastic surgeons (Izaddoost and Withers, 2012; Juhl, Koudahl and Damsgaard, 2012; Bota *et al.*, 2019; Kamel *et al.*, 2019). Juhl *et al.* emphasized the benefits of early interdisciplinary teamwork especially with NPWT treatment since longer delays before the final decision-making are prone to develop (Juhl, Koudahl and Damsgaard, 2012).

However, some cardiothoracic surgeons considers flap reconstructions, including pectoralis major muscle flaps, omentum, and even rectus abdominis and latissimus dorsi (LD) muscle flaps, as procedures that all properly trained cardiac surgeons should be able to perform with no need for plastic surgeons (Kaul, 2017).

2.3.1 Evolvement of treatment strategies

The conventional treatment of DSWI included open daily irrigation and open packing. These methods, widely used with other kinds of open wounds, have considerable limitations in the treatment of DSWI, because of the exposed heart and other vital organs. The mortality associated with these methods has been reported to be as high as 41% (Vos *et al.*, 2012).

In 1969, Bryant *et al.* re-introduced the technique of using continuous mediastinal lavage with antibiotic solutions through plastic catheters combined with direct wound closure (Bryant, Spencer and Trinkle, 1969). This technique was first described by Schumacker *et al.* in 1963 in two patients (Shumacker and Mandelbaum, 1963).

There are several recent reports emphasizing the usefulness of this suction-irrigation drainage in closed wound with minor modifications, some with excellent results (Merrill *et al.*, 2004; Molina, Nelson and Smith, 2006; Deschka *et al.*, 2013; Vos *et al.*, 2014; Dubert *et al.*, 2015). Unfortunately, many of these reports have lacked a proper control group. El Oakley *et al.* suggested earlier that closed irrigation may be sufficient for patients with type I DSWI (El Oakley and Wright, 1996).

Closed drainage using redon drains, without the antibiotic irrigation, has been described as well, but seems to lead to poor survival, with a reported mortality rate of 31.7% (Mekontso-Dessap *et al.*, 2001).

Jurkiewicz *et al.* first described the treatment of DSWI with muscle flaps and omentum in 1980 (Jurkiewicz *et al.*, 1980). They used pectoralis major advancement and turnover flaps, combined with a rectus abdominis muscle flap or omentum when needed, during the years 1975−1978. The use of flaps resulted in reduced mortality and a shorter length of hospital stay. Initially, the treatment with muscle flaps was reserved for cases in which the conventional treatment, closed drainage, had failed.

The same group reported their results later with 409 patients treated with 675 regional flaps during the years 1975−1996 (Jones *et al.*, 1997). The mortality in this report was 8.1%. Up until now, this remains the largest number of patients with DSWI reported in a single paper. It should be noted that the mean hospital stay declined to as short as 12.4 days in the late period of this study, in consequence of mostly single-stage reconstructions.

2.3.2 Antibiotics

Although the surgical treatment of mediastinitis has been widely researched, the medical treatment has been more rarely evaluated. Antibiotic therapy is constantly administrated, but not standardized.

An aggressive antibiotic treatment has been recommended with the duration of treatment ranging from three to six weeks (Singh, Anderson and Harper, 2011; Dubert *et al.*, 2015) or even as long as 12 weeks, if foreign material was present (Yusuf *et al.*, 2018). In a study group of a somewhat complicated patient material from a plastic surgery department, 50 % of the patients received parental antibiotics for six weeks or more (Landes *et al.*, 2007).

It has been shown that the ability to choose culture-specific antibiotics in an early stage is beneficial to survival (Karra *et al.*, 2006). In some areas, the incidence of MRSA is high and over-represented in a patient cohort undergoing open-heart surgery. For this reason, intravenous vancomycin is the first-line empiric treatment option in some institutions. In other units, the options for empiric antibiotic include piperacillin/tazobactam and meropenem (Yusuf *et al.*, 2018).

Obesity is common in patients with DSWI and their physical characteristics should be taken into account when planning effective antibiotic dosage (Falagas and Karageorgopoulos, 2010).

2.3.3 Debridement and re-fixation

Proper debridement is a cornerstone of the treatment (Abu-Omar *et al.*, 2017). In some instances, debridement is performed as an independent procedure before the final reconstruction. This is called a two-stage procedure. Another option is a single-stage procedure combining the debridement and flap reconstruction during the same operation.

The importance of thorough debridement of all infected and devitalized tissue has been emphasized in almost all studies concerning the treatment of DSWI, however, controversies remain. An operation technique described by Molina *et al.* constituted an exception. In their approach all sternums were re-fixated with reinforced osteosynthesis, even if the bone appeared dead, non-vascularized, or infected (Molina, Nelson and Smith, 2006).

In some centers total sternectomy is the method of choice (Schroeyers *et al.*, 2001; Kobayashi *et al.*, 2011), while in others every measure possible to preserve sternum is undertaken. In some centers, all the wires, which could serve as infected foreign bodies, are removed during the first debridement whereas in others only affected wires are removed, leaving the sternum partially closed.

Although mostly considered as a fundamental part of treating DSWI, the role of re-fixation is not without debate. Re-fixation can potentially prevent tearing of the right ventricle by moving sternal edges. Another putative benefit is enhanced pulmonary function, with a potentially limited intubation time.

Reconstruction without any re-fixation as a routine has been described by many authors (Simunovic *et al.*, 2013; Zeitani *et al.*, 2013; Wettstein *et al.*, 2014; Spindler *et al.*, 2019; Arsalan-Werner *et al.*, 2020; Piwnica-Worms *et al.*, 2020). In many of these centers, muscle flap reconstruction is considered as an alternative to re-fixation. If the sternum is left open, there is no need to leave any foreign material in the previously infected wound. On the other hand, some authors have recommended re-fixation for all patients (Molina, Nelson and Smith, 2006; Sjogren *et al.*, 2011). Circumstances that would advocate sternal resection include a poorly vascularized and fragmented sternum, as well as previous BIMA grafting in elderly or multimorbid patients (Immer *et al.*, 2005).

The functional results of leaving the sternum without fixation are also controversial. Zeitani *et al.* found considerable better results with muscle flap reconstruction alone compared to re-fixation, in terms of pain and pulmonary function (Zeitani *et al.*, 2013). In a study of Daigeler *et al.,* extension of the sternal debridement or sternectomy were not directly connected to decreased muscle strength or decreased pulmonary function (Daigeler *et al.*, 2009). However, long-term functional problems with an unstable chest, reduced mobility and limited power of the shoulder, and pain, have been reported (Eriksson *et al.*, 2011).

A current standard technique for re-fixation, and for initial sternal closure as well, remains the cerclage stainless steel wires. However, when mechanical stress is concentrated in the steel wires, they may cut into the bone, and this can lead to motion between sternal edges. This may lead to sternal dehiscence and further infection. For these reasons some consider steel wires to be an inadequate fixation method. The benefits of the conventional wire fixation include rapid access to sternal cavity in case of a postoperative bleeding, compared to plate reconstruction.

In 1977, Robicsek *et al.* described a technique which offered additional support with parasternal running wire sutures combined with several peristernal sutures (Robicsek, Daugherty and Cook, 1977). The use of this technique, or a modification of it, was described later to achieve good results (Molina, Nelson and Smith, 2006; Sjögren *et al.*, 2008).

A re-fixation using reconstruction plates with locking screws was described by Cicilioni *et al.* (Cicilioni, Stieg and Papanicolaou, 2005). They associated the use of plates with earlier extubation and a more physiological respiratory mechanism. However, in another study reported by Gaudreau *et al.*, a plating technique carried a 9.8% risk of recurrent infection, associated with MRSA and prolonged intubation (Gaudreau *et al.*, 2010).

Fawzy *et al.* described a restoration of sternal wall stability with a transverse locking plate fixation system that achieved stabilization only on the anterior surface of the ribs (Fawzy *et al.*, 2011). In this approach, no dissection was necessary below the sternum and the risk of injury to the heart was avoided. This technique was also recommended when only little sternum is left for fixation.

Most recently, an antibiotic loaded porous ceramic implant has been described as an option for sternal replacement and stabilization. It might be considered if the sternum has been totally destroyed by an infection or repeated debridement (Tricard *et al.*, 2020).

Nonetheless, while used as a standard procedure in osteosynthesis in other parts of the body, sternal fixation by plates has remained a less common fixation method in the treatment of DSWI. The experience and preferences of the surgeon likely impacts on the selection of the reconstructive method. However, more wires have been commonly used with more obese patients (Rupprecht and Schmid, 2013).

2.3.4 Use of flaps

It is a recognized plastic surgical principle, that infected and non-healing areas are treated with well vascularized flaps, such as muscle flaps and omentum.

The use of flaps in treatment of DSWI has been shown to decrease the rate of mortality, morbidity, and chronic infections. Pectoralis major muscle flap, rectus abdominis muscle or musculocutaneous flap, omentum, LD muscle or musculocutaneous flap, as well as their multiple combinations have all been used in sternal reconstruction. More recently, fasciocutaneous flaps, such as deep superior epigastric perforator (DSEP) flap and internal mammary artery perforator (IMAP) flap, have been introduced in the treatment of DSWI. All these flaps have some disadvantages, such as a lack of volume, inadequate reach to cover the entire sternum, and donor site morbidity. They also carry multiple potential complications, including functional deficits, pain, seromas, and hernias. Appropriately, it has been said that "the ideal flap does not exist" (Davison *et al.*, 2007). No significant differences in outcomes have been demonstrated. After considering the disadvantages and complication risks, it should be noted, that all the regional flaps used to cover mediastinal defects are highly reliable. Total flap necrosis is very rarely reported, as demonstrated by Jones *et al.* who described 675 regional flaps and no flap losses (Jones *et al.*, 1997).

A classification system for management of DSWI was introduced by van Wingerden *et al.* based on a thorough literature search and results from 78 papers (van Wingerden *et al.*, 2014). In this system, infections were classified into four categories depending on sternal stability, sternal bone stock, and viability of the bone. Type 1 consists of minimal bone loss and a relatively stable sternum. In these cases, NPWT has been recommended along with antibiotic dosing adjustments for obese patients, and patients with IMA harvesting. In Type 2 there is sufficient bone stock, and the sternum is relatively stable. Direct closure with possible pectoralis advancement was recommended as an option for patients with an early diagnosis, otherwise NPWT was proposed as a bridge to reconstruction. In Type 3, the sternum is unstable, but sufficient bone stock is left to allow re-fixation. Rigid fixation with wires, plates, or clips with or without flap coverage (bilateral pectoralis major muscle flap or omentum) was recommended. In Type 4, viable bone is lost, and the omentum was preferred. The authors stated that there was no Level A evidence concerning the treatment of DSWI (van Wingerden *et al.*, 2014). This means that no data is available from multiple randomized clinical trials.

There are many institutional and geographical differences in the treatment strategies. Preferences and experience of the surgeon, size and location of the wound, presence of bony deficits, as well as availability and quality of the donor site are some of the factors that influence the decision (Schols *et al.*, 2011). Prior operations and general condition of the patient need to be considered as well.

In many of the proposed algorithms, a pectoralis major muscle flap, with its different modifications, has been proposed for upper and central sternal defects (Greig *et al.*, 2007; Izaddoost and Withers, 2012; Berg and Jaakkola, 2013; Spartalis *et al.*, 2016; Piwnica-Worms *et al.*, 2020). Some prefer advancement flaps for critically ill, unstable patients (Zahiri *et al.*, 2013).

For lower sternal defects, rectus abdominis either alone or in combination with a pectoralis major muscle flap is recommended by some authors (Greig *et al.*, 2007; Piwnica-Worms *et al.*, 2020) and omentum by others (Izaddoost and Withers, 2012; Spartalis *et al.*, 2016). LD is another option for these defects, especially with previous BIMA harvesting (Berg and Jaakkola, 2013).

Table 7. Flap options to treat DSWI

Type of flap	**Blood supply**	**Benefits**	**Disadvantages**
Pectoralis major turn-over flap	IMA / intercostal perforators	Easy, local	Limited muscle bulk, possibility to functional defect
Split pectoralis major flap	IMA / intercostal perforators	Easy, local	Requires intact IMAs
Pectoralis major advancement flap	Thoracoacromial vessels	Easy, local	Limited reach to caudal sternum
Rectus abdominis flap	Epigastric vessels	Muscle bulk	Risk of herniation
Latissimus dorsi muscle flap	Thoracodorsal vessels	Muscle bulk	Limited reach, position change
Omentum	Gastroepiploic vessels	Rich vascularity	Laparotomy, risk of herniation
IMAP	IMA	Local	Requires intact IMAs
DSEP	Epigastric perforators	Limited donor site defect	Technically challenging
Free flaps	Various options	Sufficient bulk, good vascularity	Operation length, technically challenging

2.3.5 Timing of the flap reconstruction

Whether to perform flap reconstruction in one-stage or two-stages, with or without NPWT or other preconditioning of the wound, is heavily debated and without uniform conclusion.

Studies advocating one-stage reconstruction have mainly been published before the widesread adoption of NPWT in the treatment of DSWI, although there are some exceptions (Jones *et al.*, 1997; Brandt and Alvarez, 2002; Ascherman *et al.*, 2004; Karra *et al.*, 2006; Cabbabe and Cabbabe, 2009; Chittithavorn *et al.*, 2011; Jang *et al.*, 2012). The proposed benefits of immediate reconstruction include shorter hospitalization and lower mortality (Kamel *et al.*, 2019). The potential benefits of preventing ruptures of the exposed heart and grafts have been speculated (Lindsey, 2002).

Two-stage or delayed closure is favored because of the possibility to decrease wound complications (Lindsey, 2002), although in some reports prolonged NPWT was associated with flap related complications as well (Wyckman *et al.*, 2020). A two-stage approach may be preferable in patients with severe hemodynamic instability or large purulent collections that extend beyond the mediastinum (Ascherman *et al.*, 2004). Delayed closure has been associated with an increase in the rate of chronic infections and late mortality (Sjögren *et al.*, 2008; Lo *et al.*, 2014). However, selection bias must be considered, since initially more serious infections are more likely to require delayed reconstruction.

In some centers, microbiological culture samples and C-reactive protein (CRP) values are used to guide the timing of the reconstruction (Gustafsson *et al.*, 2002; Sjögren *et al.*, 2006; Rupprecht and Schmid, 2013; Pan *et al.*, 2020). However, it has been claimed that negative microbiological cultures are not mandatory before closure and are not connected to number of re-admissions, length of hospital stay, complication rates, or mortality (Biefer *et al.*, 2012; Arsalan-Werner *et al.*, 2020).

In some areas the access to flap reconstruction requires a referral to a department of plastic surgery, which can be remotely located. This may lead to delays in referral. An unbelievable average delay of 317 days after initial sternotomy was reported by Daigeler *et al.* (Daigeler *et al.*, 2009). In their report Landes *et al.* stated that 60% of their patients had undergone one attempt of sternal closure by thoracic surgeons before referral to plastic surgery (Landes *et al.*, 2007). Wong *et al.* postulated that referral to the plastic surgery department within 48 hours of diagnosis of DSWI resulted in fewer cases of chronic osteomyelitis (Wong *et al.*, 2006). However, later referral was not associated with complications in a trial conducted by Landes *et al.* (Landes *et al.*, 2007).

2.3.6 Pectoralis major muscle flaps

Pectoralis major muscle remains as the most common flap option in sternal reconstructions. This flap possesses multiple benefits including consistent vascularity, multiple vascular pedicles, and proximity to the wound. Raising the flap does not require additional incisions, the operation time is short, and the flap is straightforward to dissect.

The pectoralis major muscle flap can be mobilized either as an advancement flap based on the thoracoacromial vessels, or as a turn-over flap based on the internal mammary vessels. The flap can be raised unilaterally or bilaterally with many modifications having been described.

The IMA must be intact if one wishes to use pectoralis major as a turn-over flap. With turn-over flaps, the humeral insertion of the muscle is divided, and this may lead to a functional defect. However, other factors, such as stabilization of the sternum, have been reported to contribute to the functional result as well (Eriksson *et al.*, 2011). The lateral portion of the turn-over flap is folded into the defect. In some instances, this may result in a contour deformity of the chest and tension on skin closure. Other cosmetic disadvantages include depression at the donor site and possible distortion of the breast in female patients (Li *et al.*, 2004). The skin is usually closed directly, but in some cases skin grafts may be needed. Dividing the humeral insertion also violates the anterior axillary fold. Sometimes a separate incision laterally is used to release the humeral insertion (de Souza Horácio *et al.*, 2017). However, in their study material with some potential confounding factors, Zahiri *et al.* described fewer complications with a turn-over flap as compared to an advancement flap (Zahiri *et al.*, 2013). The opposite finding was reported by Kamel *et al.* with more flap necrosis in turn-over flaps (Kamel *et al.*, 2019).

Advancement flaps are commonly used bilaterally, in order to sufficiently obliterate the dead space (Wong *et al.*, 2006; Song and Liu, 2020). However, in some cases unilateral advancement flaps seem to be sufficient (Lo Torto *et al.*, 2020). This may be recommended in cases when only minimal debridement is needed, and the sternum is re-fixated (Kaye *et al.*, 2010). A unilateral advancement rotational muscle flap may also be sufficient, if the humeral attachment is released (de Souza Horácio *et al.*, 2017; Wyckman *et al.*, 2020).

The advancement flap may be dissected as a muscle-only rotation flap (Jang *et al.*, 2012) or as musculocutaneous flaps. When used as musculocutaneous flaps, dividing the humeral attachment may not be necessary. Without humeral detachment only a minimal shoulder weakness is noticed (Jang *et al.*, 2012; Song and Liu, 2020). With musculocutaneous flaps, undermining of the skin and subcutaneous tissue over the muscle is usually kept to a minimum (Cicilioni, Stieg and Papanicolaou, 2005). A limited mobilization of a musculocutaneous flap up to eight centimeters from the midline has been described (Tewarie *et al.*, 2019).

When bilateral flaps are used, it is possible to bury one flap beneath the other to gain more muscle bulk to the midline, especially when the re-fixation is not possible. With advancement or rotation flaps the widest part of the pectoralis muscle is used to cover the wound. A modification of bilateral advancement flaps using only partial muscle flaps for a patient with a localized infection and limited debridement was described by Preminger *et al.* (Preminger, Yaghoobzadeh and Ascherman, 2014).

With unilateral flaps, it is advisable to raise the flap on the non-dominant side. However, sparing pectoralis major with an intact IMA for further use may be more important when raising a unilateral advancement flap (Kaye *et al.*, 2010).

The advancement flaps may have insufficient reach for the most caudal third of the sternum (Spartalis *et al.*, 2016). This is also the most common site for dehiscence after flap reconstruction (Li *et al.*, 2004; Davison *et al.*, 2007; Spartalis *et al.*, 2016). For this reason, some authors have combined advancement flaps with other flaps when a caudal third of the sternum is affected, although others have considered this unnecessary (Ascherman *et al.*, 2004). There are several ways to address the issue of the lower sternal defect, for example, using the split pectoralis major muscle flap (Lindsey, 2002; Li *et al.*, 2004; Brown *et al.*, 2017) or combining the anterior rectus fascia extension with a pectoralis major muscle flap (Davison *et al.*, 2007). A combination of pectoralis major and rectus abdominis muscle flaps raised together has also been described (Greig *et al.*, 2007).

The segmental perfusion via IMAP allows the muscle to be split into two or three subunits that are tailored into the defect (Lindsey, 2002; Li *et al.*, 2004; Brown *et al.*, 2017). The most important benefit of this flap modification is better coverage to the lower third of the sternum. A technique described by Brown *et al.* utilized the upper half of the muscle as an advancement flap and the lower third of the muscle as a turn-over flap (Brown *et al.*, 2017). Li *et al.* used the whole pectoralis muscle split into two or three parts by the muscle fibers to be used as turn-over flaps (Li *et al.*, 2004).

Common complications, in addition to the dehiscence in the lower part of the sternum, include hematoma and seroma (Davison *et al.*, 2007; Lo Torto *et al.*, 2020; Wyckman *et al.*, 2020). Other described complications include intense transient pain, chronic pain, dysesthesia, and granuloma (Milano *et al.*, 1999; Daigeler *et al.*, 2009; de Souza Horácio *et al.*, 2017).

More rarely used modifications include a pectoralis major muscle flap combined with rotationplasty of the breast (Schols *et al.*, 2011) and an infra-areolar pectoralis major island myocutaneous flap based on the thoracoacromial artery (Simunovic *et al.*, 2013).

2.3.7 Omentum

The benefits of the omentum include its rich blood and lymphatic supply. It contains immunologically active cells which can provide anti-infective properties. There is also some neovascularization potential that, along with the rich vascular supply, is beneficial in achieving higher concentrations of antibiotics at the infection site. The omentum is pliable and has a good reach as it has a relatively long vascular pedicle which enables the flap to reach up to the superior aspect of the sternotomy incision. However, the dimensions of this flap may vary considerably, especially after prior abdominal surgery.

Prior extensive abdominal surgery is mostly considered as a relative contraindication. The conditions, such as potential adhesions, cannot be determined preoperatively and in some cases the omentum may be lacking altogether. However, successful use of the flap after previous abdominal surgery has been described (Acarturk *et al.*, 2004).

The need of laparotomy carries the risk of spreading the infection. An incidence of hernia, including abdominal wall hernia and diaphragmatic hernia, as high as 20%, has been reported in some trials (Milano *et al.*, 1999; Schroeyers *et al.*, 2001; Schols *et al.*, 2011). Other described complications include necrosis of the transverse colon and calcification (van Wingerden *et al.*, 2010; Hashimoto *et al.*, 2015).

Chittithavorn *et al.* reported good results from immediate omentum reconstruction with a short operation time and few complications (Chittithavorn *et al.*, 2011). Slight numbness of the sternal skin and minor paradoxical chest movement was described. However, paradoxical movement of the chest may be transient (Athanassiadi *et al.*, 2007). If sternectomy is needed, an omental flap does not offer chest wall stability. In a one-year follow-up, every third patients reported pain, numbness, and a sense of sternal instability (Parissis *et al.*, 2011).

In order to limit the donor site defect and complication risks, laparoscopic techniques have been utilized (Acarturk *et al.*, 2004; van Wingerden *et al.*, 2010). A laparoscopic harvest technique may cause less harm to the abdominal wall, preserve respiratory function, and limit exposure of the second body cavity. Furthermore, it may evoke less abdominal pain and less scarring (van Wingerden *et al.*, 2010). A conversion to an open technique may sometimes be needed because of adhesions from some previous abdominal surgery (Acarturk *et al.*, 2004). Puma *et al.* introduced a laparoscopic technique using only part of the omentum, in such a way that neither of the gastroepiploic vessels needed to be ligated, as in their experience, the whole omentum tended to be bulky (Puma *et al.*, 2003).

When the omentum is raised with an open technique, the length of the laparotomy incision should be kept to a minimum. Some surgeons prefer a separate incision (Milano *et al.*, 1999; Chittithavorn *et al.*, 2011) while a small extension of the sternotomy incision is preferred by others (Athanassiadi *et al.*, 2007). However, even with an open approach, the incision can be limited to less than that required to lift the rectus abdominis muscle flap (Izaddoost and Withers, 2012).

Omentum has a dual blood supply from a vascular arcade formed by the right and the left gastroepiploic vessels. Either one of these vessels can be used to raise the flap according to surgeon's preference, although the right gastroepiploic artery is often preferred because it is larger (Francel and Kouchoukos, 2001; Kaye *et al.*, 2010; de Brabandere *et al.*, 2012). The left gastroepiploic artery, however, lies closer to sternal defect and may be preferable when extra length is needed.

Different routes from abdominal cavity to the sternal defect have been described. A transdiaphragmatic route has been considered to reduce operative time, bleeding, and trauma (de Brabandere *et al.*, 2012; Vyas, Prsic and Orgill, 2013). This route is also more direct adding some length to the flap and has been claimed to reduce the rate of hernias. Transabdominal tunneling through the abdominal fascia is recommended by some authors, because the possible herniation is easier to diagnose (Stump *et al.*, 2010).

The omental flap can be covered with pectoralis major advancement flaps, a vast undermining of the sternal skin, or free skin graft (Acarturk *et al.*, 2004; Stump *et al.*, 2010; Schols *et al.*, 2011; Van Wingerden, Lapid and Totté, 2013). The rich vascular supply enables the flap to support a skin graft easily. When omentum is totally buried under muscle, the flap monitoring is more challenging (Van Wingerden, Lapid and Totté, 2013).

The role of omentum in covering sternal defects varies. It is considered as a salvage flap in many institutions but has many indisputable benefits as well. It has been recommended when there is a predicted difficulty with infection clearance, and for use in diabetic patients (Stump *et al.*, 2010). Van Windergen *et al.* recommended omentum especially for patients with El Oakley IV mediastinitis (Van Wingerden, Lapid and Totté, 2013). The omentum may also be a first choice when prosthetic material is exposed (Francel and Kouchoukos, 2001; Piwnica-Worms *et al.*, 2020) and in patients with a candida infection (Francel and Kouchoukos, 2001). Kaye *et al.* used omentum in cases with large and deep defects, where otherwise multiple muscle flaps would be needed (Kaye *et al.*, 2010).

Best evidence topic from van Windergren *et al.* in 2011 reviewed 16 studies comparing muscle flaps and an omental flap (Van Wingerden *et al.*, 2011). It seems that the omental flap may be preferable in terms of mortality and morbidity. The most feared major complications related to omental flap, such as hernias and contamination of peritoneal space, seemed to be rare.

The omentum has been commonly covered by bilateral myocutaneous pectoralis major advancement flaps (Brandt and Alvarez, 2002; Chittithavorn *et al.*, 2011; de Brabandere *et al.*, 2012). Izaddoost *et al.* also combined omentum with a pectoralis major muscle flap in the treatment of large defects by splitting the omentum with one part on top and the other beneath of the pectoralis flap (Izaddoost and Withers, 2012). Some rare variations of the omental flap, such as using transomental titanium plates for sternal stabilization (Sansone *et al.*, 2011) and combining an omental flap with closed irrigation with vancomycin (Hirata *et al.*, 2003), have been described. Converting omentum into a free flap because of disruption of the pedicle, has been described as well (Acarturk *et al.*, 2004). One of the most extensive repair techniques, after destruction of the sternum, utilized an omental flap, a titanium mesh, and a rectus abdominis flap in a sandwich model (Zor *et al.*, 2014).

2.3.8 Rectus abdominis muscle flap

The rectus abdominis muscle flap is mostly used for the defects in the most caudal third of the sternum (Davison *et al.*, 2007). It is also used as a secondary option if a pectoralis flap is unavailable. Its advantages include good volume of the muscle tissue. Rectus abdominis can be used as a muscle or as a musculocutaneous flap. The vascular supply is based on the superior epigastric artery. The flap may be unreliable and is not recommended if the ipsilateral IMA has been harvested in the primary CABG. Subcostal incisions have been also considered as contraindications.

However, there have been some case reports describing the use of a rectus abdominis muscle flap even when the IMA has been previously harvested. In these instances, circulation to the superior epigastric vessels was based on a collateral circulation through the musculophrenic artery and lower intercostal arteries. A delay phenomenon is speculated to promote the development of the collateral circulation. However, using the rectus abdominis without an intact IMA, should be limited and requires careful consideration (Netscher, Eladoumikdachi and Goodman, 2001).

Common complications include wound healing problems at the donor site, dehiscence of the abdominal wound, as well as flap tip necrosis and subsequent dehiscence of the upper part of the sternal wound (Davison *et al.*, 2007).

Possible late complications include herniation (Jones *et al.*, 1997) and worsening of the lung function. It may be possible to diminish the risk of herniation by leaving the rectus fascia in place with a two-layer closure (Davison *et al.*, 2007). In addition, the risk of hernia may have been overestimated; for example Francel *et al.* reported good results with 50 rectus flaps and zero hernias (Francel and Kouchoukos, 2001).

A bipedicle flap combining pectoralis major and rectus abdominis muscle, also called a robust flap, was described to treat defects of the lower sternum or comprising the whole length of sternum (Greig *et al.*, 2007; Roh *et al.*, 2008). This flap had a dual blood supply from the thoracoacromial artery and the deep inferior epigastric artery. Chou *et al.* raised this bipedicle flap with endoscopic assistance aiming at limited abdominal wall morbidity (Chou *et al.*, 2016).

2.3.9 Latissimus dorsi (LD) muscle flap

LD muscle or musculocutaneous flaps are rarer reconstructive options usually saved for salvage procedures (Francel and Kouchoukos, 2001). However, there are centers that use these flaps as a first line option to cover sternal defects (Bota *et al.*, 2019; Spindler *et al.*, 2019).

An LD flap is most often used for defects of the upper two-thirds of the sternum. Advantages include saving the collateral blood supply of the sternum and parasternal tissues. The muscle bulk usually exceeds that of a pectoralis muscle flap and the vascular supply is constant through thoracodorsal vessels.

Disadvantages include poor reach to the caudal third of the sternum. Although it has often been speculated that the operation demands a repositioning and is therefore time demanding, performing the operation with the patient in his/her side position is an option (Spindler *et al.*, 2019).

Complications include donor site seroma, which is very common affecting as many as 74% of the patients (Bota *et al.*, 2019), and donor site dehiscence.

However, in terms of muscle strength, no late donor site defects usually arise (Spindler *et al.*, 2019). If possible, the non-dominant hand side is used (Bota *et al.*, 2019).

An LD flap can be also converted into, or used as, a free flap (Taeger *et al.*, 2016).

2.3.10 Internal mammary artery perforator (IMAP) flap

The vascular anatomy of internal mammary artery perforator (IMAP) flap has been thoroughly studied by cadaveric dissections, angiograms, and computed tomographic angiograms. Its vascular anatomy is constant resulting in a highly reliable flap (Vesely *et al.*, 2007; Schmidt *et al.*, 2010; Gillis, Prasad and Morris, 2011; Paes *et al.*, 2011). The dominant perforator, usually located in the second intercostal space, vascularizes an area from the clavicle to the xiphoid and from a midsternal to the anterior axillary fold (Vesely *et al.*, 2007; Paes *et al.*, 2011). Direct closure is usually possible with flaps up to six centimeters of width, although flaps up to 13x20cm have been described (Schmidt *et al.*, 2010).

The use of an IMAP flap has previously been described in head and neck reconstructions and to cover sternal defects, for example, after tumor resections (Vesely *et al.*, 2007). Instead, its use for sternal defects after DSWI has been rarely reported. Kannan *et al.* used the IMAP flap in fasciocutaneous and musculocutaneous forms to cover sternal dehiscence after sternotomy in seven patients (Kannan, 2016). Koulaxouzidis *et al.* used the IMAP fasciocutaneous flap in nine patients after DSWI (Koulaxouzidis *et al.*, 2015). Simultaneous use of the fifth IMAP flap and a unilateral breast reductionplasty has been described in a case report (Tadisina *et al.*, 2017).

2.3.11 Other fasciocutaneous flaps

Traditionally muscle flaps are preferred to cover osteomyelitis or deep infected spaces. Lately, however, the use of fasciocutaneous flaps instead of conventional muscle flaps in the treatment of osteomyelitis has been investigated (Salgado *et al.*, 2006).

The use of a superior epigastric artery perforator flap after sternal osteomyelitis was described by Wettstein *et al.* (Wettstein *et al.*, 2014). It should be noted that in this material, all patients were obese and thus the usefulness of this flap for deep defects in patients with normal or low body mass index (BMI) has not been verified.

A reconstruction of a sternal defect with a bilateral local tunneled fasciocutaneous flap from inferomedial breast was described by Coopera *et al.* (Coopera and Paynea, 2014) with a concurrent reductionplasty to limit the tension that is directed to the wound.

2.3.12 Free flaps

Free flaps are rarely needed in the reconstruction after DSWI. They are most often required in patients with whom other flap options have been already used or are not available. As pointed out by Dornseifer *et al.*, this is in contradiction with the usage of free flaps in other parts of the body (Dornseifer *et al.*, 2016). This may be due to the lack of suitable recipient vessels and the multimorbidity of the patient group. However, when other options fail, free tissue flap reconstruction can provide a fair amount of well-vascularized tissue.

Traditionally, arterio-venous loops have been used when recipient vessels are lacking at a site. An arterio-venous loop can be formed by connecting the cephalic vein to the thoracoacromial artery or by connecting the saphenous vein to the subclavian vessels (Reichenberger *et al.*, 2010; Taeger *et al.*, 2016).

The gastroepiploic vessels may be used as a recipient site (Dornseifer *et al.*, 2016). This technique makes possible the use of the omentum as a flow-through flap if an excessive amount of tissue is needed. Other recipient vessels may be found from the neck (Francel and Kouchoukos, 2001).

Taeger *et al.* recommended free flap reconstruction, when more than one local flap would otherwise be needed (Taeger *et al.*, 2016). In addition, they preferred free flap over the omentum because of fewer complication risks in terms of the donor site. In addition, raising a free flap in experienced hands was not necessarily a longer operation compared to the harvesting of the omentum.

Taeger *et al.* preferred the lower limbs as the donor site because this spared the respiratory muscles (Taeger *et al.*, 2016). In addition, they recommended muscle flaps, such as vastus lateralis and rectus abdominis, over fasciocutaneous flaps, such as anterolateral thigh flap, because of the rich vascular supply in the muscle tissue. Reichenberger *et al.* used tensor fascia lata, whenever feasible, as a free flap, because it provided a reliable skin flap with a large area of vascularized fascia (Reichenberger *et al.*, 2010). Francel *et al.* used LD and rectus abdominis as a free flap in some cases, for example, when bilateral subcostal incisions prevented the use of a rectus as a pedicled flap (Francel and Kouchoukos, 2001).

2.3.13 Complications of flap reconstruction

The rate of complications often seems high in most of the publications in this field. Many of the patients undergoing open-heart surgery, and suffering from subsequent DSWI, are elderly, possibly obese, and have multiple comorbidities. The patients' baseline characteristics are further worsened by recent cardiac surgery and the potentially instable sternum.

In a series examining 409 patients with mediastinitis Jones *et al.* estimated a 25.3% overall complication rate after flap surgery with multiple flap choices (Jones *et al.*, 1997). Major complications needing operative treatment have been reported in around 16% of flap reconstructions (Zahiri *et al.*, 2013; Piwnica-Worms *et al.*, 2020). However, total flap loss is a rare event (Jones *et al.*, 1997; Izaddoost and Withers, 2012). In a relatively large retrospective analysis conducted by Francel *et al.*, most patients were satisfied with the cosmesis and were able to return to preoperative hobbies, sports, and employment (Francel and Kouchoukos, 2001). Muscle weakness was reported by 20% of the patients.

The presence of multiresistant bacteria significantly increased the risk of complications after flap reconstruction (Piwnica-Worms *et al.*, 2020). Diabetes increased the dehiscence rate after reconstruction (Landes *et al.*, 2007) and has been reported to elevate the risk of re-operation by as much as nine-fold (Li *et al.*, 2004). Hypertension, a history of smoking, and septicemia have also been associated with flap related complications (Jones *et al.*, 1997).

There have been some retrospective comparative studies to evaluate the role of iNPWT to prevent surgical complications after sternal flap reconstructions (Lo Torto *et al.*, 2017; Rashed *et al.*, 2017; Nickl *et al.*, 2018). In a study with 30 patients in the intervention group treated with Prevena™, the complication rate declined from 37.5% to 13% and the major complication rate from 15% to 3% (Lo Torto *et al.*, 2017). In a study with 19 patients treated with Prevena™, the rate of major complications was reduced from 32.1% to 5.3% (Nickl *et al.*, 2018). A small study with 10 patients using the Vivano System™ detected a decrease in the hospitalization length (Rashed *et al.*, 2017). It should be noted that historical control group was used in all these studies.

2.3.14 Negative pressure wound therapy (NPWT)

The technique of NPWT in the treatment of open wounds was first described by Chariker *et al.* in 1989. NPWT was introduced in the treatment of DSWI by Obdeijn *et al.* in 1999 (Obdeijn *et al.*, 1999). In their patient series NPWT was used as a single therapy without subsequent flaps.

In 2001, Hersh *et al.* recommended the use of NPWT as a substitute to open packing before muscle flap reconstruction, especially for those patients in whom one-stage reconstruction was not feasible (Hersh *et al.*, 2001). They noted an improvement in sternal wound stabilization during the perioperative period, and a shorter length of mechanical ventilation.

Many reports using NPWT in treatment of DSWI followed quickly. The first studies were case series without control groups, but reporting promising results (Tang, Ohri and Haw, 2000; Gustafsson *et al.*, 2002; Domkowski *et al.*, 2003; Gustafsson, Sjögren and Ingemansson, 2003; Luckraz *et al.*, 2003; Song *et al.*, 2003). NPWT rapidly gained widespread acceptance. The benefits of NPWT include decreased edema, controlling of wound exudate, fewer dressing changes, improved patient comfort, and accelerated mobilization. However, some hesitation to use NPWT in cases with an acute infection remained (Tarzia *et al.*, 2014).

2.3.15 Technique and mechanisms of NPWT

A commercial NPWT setting includes a polyurethane foam that is fitted into the defect. The foam is covered superficially by an adhesive film and connected to a canister with an evacuation tube. A portable pump is used to apply continuous negative pressure to the wound with excess fluid being collected into the canister thus reducing tissue edema. Several commercial NPWT systems are currently available.

The heart is protected with a bottom layer of white non-adhesive foam or sufficient layers of paraffin gauzes to prevent adhesion formation and ventricular rupture (van Wingerden, Segers and Jekel, 2011; Gudbjartsson *et al.*, 2016; Waked *et al.*, 2018). The polyurethane foam is inserted between the sternal edges and a second layer is inserted between the skin edges when needed (Waked *et al.*, 2018). The dressings are changed around every third day. Changing the dressings may occur in the operating room (Sjögren *et al.*, 2008) or bedside on the ward, depending on institutional routines, the pain and discomfort experienced by the patient, and the need for further debridement.

There are numerous proposed mechanisms to explain how NPWT can accelerate wound healing, e.g. arteriolar dilatation, increased blood flow, stimulated angiogenesis, as well as induced cell proliferation and tissue granulation (Chen *et al.*, 2005; Morykwas *et al.*, 2006; Ichioka *et al.*, 2008; Mouës, Heule and Hovius, 2011). It has been speculated that there is a modulation of cytokines towards an anti-inflammatory profile, and activation of mechanoreceptor and chemoreceptor-mediated cell signaling (Glass *et al.*, 2014). Other proposed mechanisms include reduced wound edema, continuous wound drainage, approximation of wound edges, protection from external pathogens, and increased bacterial clearance.

The proposed advantages distinctive to the sternal area include sternal wall stabilization and improved respiratory mechanics. Stimulation of blood flow in peristernal area has been studied (Petzina *et al.*, 2006). A porcine model was used to analyze the safety of NPWT in terms of central hemodynamics and respiratory functions. Pressures between -50 - -185mmHg were considered safe without compromise in either parameter (Sjögren *et al.*, 2004; Gustafsson *et al.*, 2006).

NPWT with instillation is a rarer form of NPWT in which periodical rinsing of the wound with selected fluid is combined with periodical NPWT. This kind of application of the instillation mode in the treatment of DSWI has been described in a case report (Morgante and Romeo, 2017).

2.3.16 Effectiveness of NPWT

During recent decades, in many centers, NPWT has acquired a position as the first-line option in the treatment of sternal wound infections (Agarwal *et al.*, 2005; Sjögren, Gustafsson, *et al.*, 2005; Petzina *et al.*, 2010; Deniz *et al.*, 2012). Several studies have associated NPWT with decreased mortality in comparison with conventional treatments such as closed irrigation, open daily irrigation, open packing, as well as different combinations of the above-mentioned approaches (Segers *et al.*, 2005; Sjögren, Gustafsson, *et al.*, 2005; Baillot *et al.*, 2010; Petzina *et al.*, 2010; De Feo, Corte, *et al.*, 2011; Deniz *et al.*, 2012; Vos *et al.*, 2012; Morisaki *et al.*, 2016). In a retrospective study conducted by Sjögren *et al.* examining 46 patients treated with NPWT, the early and long-term mortality remained the same when compared to patients without mediastinitis (Sjögren, Nilsson, *et al.*, 2005).

NPWT has also been associated with shorter treatment periods than needed with conventional treatments (Fuchs *et al.*, 2005; Damiani *et al.*, 2011; De Feo, Corte, *et al.*, 2011; De Feo, Vicchio, *et al.*, 2011; Yu *et al.*, 2013). Two meta-analyses have been published with controversial conclusions. Both of them, however, favored NPWT in some form or other (Damiani *et al.*, 2011; Falagas *et al.*, 2013)

Faster normalization of white blood cell counts and CRP values with NPWT compared to conventional treatments have been described (Fuchs *et al.*, 2005; De Feo, Vicchio, *et al.*, 2011). NPWT has also been associated with fever re-infections (Segers *et al.*, 2005; Steingrimsson *et al.*, 2012; Yu *et al.*, 2013; Risnes *et al.*, 2014). The effectiveness of NPWT to treat DSWI caused by MRSA and candida has been separately analyzed and confirmed (Modrau, Ejlertsen and Rasmussen, 2009; Feo *et al.*, 2010; Morisaki *et al.*, 2011; Osada *et al.*, 2012).

Nonetheless, previous studies concerning the efficacy of NPWT have been criticized about the poor quality and heterogenic nature of their control groups (Bain, Lo and Soldin, 2012; Yu *et al.*, 2013; White, Meyer and Harlin, 2019). The use of muscle flaps in the study and control groups has often varied randomly; in some studies the use of flaps was even higher in the NPWT group (Fleck *et al.*, 2004; Feo *et al.*, 2010; De Feo, Vicchio, *et al.*, 2011).

It has been previously claimed that flap reconstruction achieves distinctly better results as compared to conventional treatment methods (Jones *et al.*, 1997; Brandt and Alvarez, 2002; Karlakki *et al.*, 2013). The importance of early wound coverage has also been emphasized (Brandt and Alvarez, 2002; Karra *et al.*, 2006; Bapat *et al.*, 2008; Lo *et al.*, 2014). The first study comparing NPWT with a homogenous group treated with muscle reconstruction was published in 2019 (Barbera *et al.*, 2019). In this study, however, the flap reconstruction was performed in a delayed fashion. The first studies to compare NPWT with immediate reconstruction were only published in 2020. Although with some limitations, these studies associated NPWT with higher mortality, longer hospitalization, more impaired respiratory function, larger number of re-operations, and fungal infections (Pan *et al.*, 2020; Hämäläinen *et al.*, 2021). A review article from 2019 failed to find convincing support for the routine use of NPWT and concluded that there was a need for more accurate evaluative studies to assess the effectiveness of this treatment (White, Meyer and Harlin, 2019).

2.3.17 NPWT - a bridge to reconstruction or a single treatment modality?

In some institutions, the use of NPWT has been combined with subsequent flap reconstruction one to three weeks later (Ennker *et al.*, 2009; Baillot *et al.*, 2010; Feo *et al.*, 2010; De Feo, Vicchio, *et al.*, 2011; Morisaki *et al.*, 2011; Schols *et al.*, 2011; de Brabandere *et al.*, 2012). There are also protocols in which flap reconstruction has been used, but only after NPWT and an attempt of direct closure have failed (Juhl *et al.*, 2017). In some cases, the stiffness of pre-sternal tissue after NPWT may warrant pectoralis major advancement flaps in order to achieve skin closure (Salica *et al.*, 2014). In an overview of the management of DSWI Singh *et al.* considered that one potential role of NPWT could be as a beginning of the treatment process while the patient is referred to a plastic surgeon (Singh, Anderson and Harper, 2011).

However, it does seem that using NPWT, for some patients, is sufficient without subsequent flap reconstruction (Gustafsson *et al.*, 2002; Domkowski *et al.*, 2003; Gustafsson, Sjögren and Ingemansson, 2003; Luckraz *et al.*, 2003; Agarwal *et al.*, 2005; Cowan *et al.*, 2005; Fuchs *et al.*, 2005; Immer *et al.*, 2005; Mokhtari *et al.*, 2008; Sjögren *et al.*, 2008; Atkins *et al.*, 2009; Deniz *et al.*, 2012; Lonie *et al.*, 2015). When aiming for full closure of the wound with NPWT alone, some circumstances are considered beneficial, for example, negative blood culture, deepness of the wound less than four centimeters, and sternal stability without bony exposure (Gdalevitch, Afilalo and Lee, 2010).

Zeitani *et al.* performed a propensity score matched study to compare patients who, after a period of NPWT, underwent either bilateral pectoralis major muscle reconstruction or sternal re-wiring (Zeitani *et al.*, 2013). The patients undergoing muscle reconstruction had less pain, better physical quality of life, better respiratory function, and a shorter length of hospitalization. Grapow *et al.* described the possibility to use titanium plating after the use of NPWT since this was a less invasive procedure compared to flap reconstruction and was linked with better patient satisfaction (Grapow *et al.*, 2017). However, plating was associated with more pain as compared to muscle reconstruction.

In a review article published in 2012 Juhl *et al.* reflected on whether it would be better to proceed directly to major reconstruction or to favor a longer treatment with NPWT in order to achieve a more limited reconstruction (Juhl, Koudahl and Damsgaard, 2012). Although the prospect of performing a multicentric randomized study to compare the two applications of NPWT, with or without subsequent flap reconstruction, has been proposed a decade ago (Berdajs *et al.*, 2011), the matter remains to be unsolved.

2.3.18 Complications of NPWT

Although NPWT has been considered to be a rather safe option (Agarwal *et al.*, 2005; Sjogren *et al.*, 2011), there have been a number of studies reporting severe complications such as bleeding (Gustafsson, Sjögren and Ingemansson, 2003; Sartipy *et al.*, 2006; Sjogren *et al.*, 2011; van Wingerden, Segers and Jekel, 2011; Vos *et al.*, 2013; Risnes *et al.*, 2014; Salica *et al.*, 2014) and potentially lethal right ventricular rupture (Fuchs *et al.*, 2005; Ennker *et al.*, 2009; van Wingerden, Segers and Jekel, 2011; Risnes *et al.*, 2014). The presence of sufficient layers of paraffin gauze dressing covering the heart has been proposed to prevent these complications (Sartipy *et al.*, 2006; van Wingerden, Segers and Jekel, 2011).

It should be noted that ventricular rupture has also been encountered in the conventional treatment of DSWI (Arbulu *et al.*, 1996; Sjogren *et al.*, 2011). It may be caused by sharp sternal edges in cases of sternal instability. A late bleeding in a closed chest after mediastinitis due to local inflammatory processes has been reported as well (Niclauss, Delay and Stumpe, 2010). It has been speculated that NPWT may even reduce the risk of ventricular rupture by stabilizing the sternal edges.

Other problems, such as discontinuation of treatment, caused by pain (Spartalis *et al.*, 2016) or, for example, technical difficulties, have rarely been addressed. These drawbacks of NPWT have been described when utilizing NPWT in other indications (Braakenburg *et al.*, 2006). Oliveira *et al.* reported a high rate of discomfort caused by NPWT with pain being reported by every second patient (Oliveira *et al.*, 2020).

A long duration of NPWT (more than 21 days) has been associated with recurrent problems due to chronic infections, including sternal osteomyelitis (Bapat *et al.*, 2008).

3 AIMS OF THE STUDY

Our aim was to analyze the role of iNPWT and NPWT in the prevention and treatment of DSWI. In addition, we described and analyzed our results using two less common flap reconstruction options in the treatment of DSWI.

In more detail, we studied the following topics:

1. If DSWI could be prevented by using iNPWT with PICO™ (I)
2. If NPWT was a safe and effective treatment of DSWI (in comparison with early muscle flap reconstruction) (II)
3. If the use of prior NPWT and postoperative iNPWT could decrease flap related surgical complications after DSWI (IV)
4. If modified IMAP flap was useful in the treatment of DSWI (III)
5. If split pectoralis major muscle flap was a suitable option in the treatment of DSWI (IV)

4 SUBJECTS AND METHODS

4.1 MATERIALS (I-IV)

These four studies included four different study materials. All study materials were collected independently. However, these materials included several of the same patients and were cross checked to some extent. All patients were treated in the Kuopio University Hospital.

The material in study I consisted of 952 patients. The PICO group included 180 high-risk patients treated with iNPWT after CABG. The control group included 772 similar patients analyzed retrospectively. The 25 patients treated with iNPWT before the study protocol as well as 16 patients who died within 14 days after CABG were excluded. All patients had either obesity or diabetes as a risk factor.

The material in study II included 125 patients. The NPWT group consisted of 55 patients treated with NPWT as a first-line option. The early muscle flap group consisted of 60 patients treated with muscle flap reconstruction without preconditioning of the wound with NPWT. The early muscle flap closure was carried out as a one-stage reconstruction in 57 (95%) of the patients. Ten patients were treated with re-fixation and direct closure without either muscle flap or NPWT and were excluded from the analysis.

The material in study III comprised 10 patients treated with IMAP flap combined with pectoralis major muscle flap after DSWI. The material for the original article included three additional patients with the same surgical procedure after different complications of cardiovascular surgery. These patients were excluded from the analysis presented in this thesis.

The material in study IV included 82 patients treated with pectoralis major muscle flap. The study group consisted of 24 patients treated with NPWT preoperatively and iNPWT on top of the pectoralis major muscle flap. The first control group consisted of 48 patients with pectoralis major muscle flap without any form of NPWT. The second control group included 10 patients with pectoralis major muscle flap and preoperative NPWT only. This study material represented a patient series of 58 patients with split pectoralis major muscle flap.

The study protocols in studies I, II and III were separately approved by the Ethics Committee of the Kuopio University Hospital. All materials were collected, handled, and stored with care and appropriate methods were applied to protect sensitive data and identifiable material.

Table 8. Defining study materials

	Study I	Study II	Study III	Study IV
Number of patients in the study group	180	55	10	24
Study group treated in	2018-2020	2007-2018	2010-2016	2012-2020
Number of patients in the control group	772	65	-	48 + 10
Control group treated in	2012-2017	2006-2014	-	2006-2017

All retrospective study materials were gathered by first identifying suitable patients from the operating room records using diagnosis and operation codes (International Statistical Classification of Diseases (ICD10); Nordic Classification of Surgical Procedures codes). The data of these patients was then manually collected by reviewing the medical records.

The diagnosis of DSWI was set by manually reviewing the patient records, operation records, and laboratory findings.

In study I, the Kuopio University Hospital Heart Registry was used to collect the data for the control group. The most important information, including the presence of diabetes and infections, were double checked manually from the patient records. The Heart Registry was also used in study II to collect part of the information, including EuroSCORE II values and perfusion times.

The material for the study group in study I was gathered prospectively between 2018 and 2020. All high-risk patients who underwent CABG were considered as eligible. Patients were viewed as high-risk if they had BMI 31 kg/m2 or more, or a diagnosis of diabetes. All patients with diabetes were included regardless of its type, severity, or treatment. Patients with immunosuppressive therapy and patients that were not capable of giving informed consent were excluded. Patients were informed by a member of the research team on the day before the operation. After written and verbal information, voluntary written consent was gained from all the patients.

4.2 STATISTICAL METHODS (I-IV)

The statistical analyses were performed using IBM SPSS statistics 25.0/27.0 software for Windows (SPSS Inc., Chicago, IL, USA). Frequencies and percentages are reported from categorical variables. Mean values and standard deviation were utilized for continuous variables. The Mann-Whitney U test was used when comparing two unpaired groups as a non-parametric test. Fisher's exact test and Pearson's chi-squared test were used when comparing categorical variables. The Fisher's exact test was used when there were <5 expected values in any of the cells of a contingency table. In other cases, the Pearson's chi-squared test was used.

In study I, an analysis was conducted on an intention to treat basis. A propensity score analysis was also performed in the study I. A caliber matching with a width of 0.2 x SD was used. When calculating the propensity scores, the following clinically significant covariates were considered: age, gender, type of original heart surgery, presence of unstable angina pectoralis, diabetes, diabetes type one, kidney disease, chronic lung disease, peripheral artery disease, smoking, previous myocardial infarction, BMI, and EuroSCORE II value.

4.3 DIAGNOSIS OF DSWI (I-IV)

The diagnosis of DSWI was determined according to the guidelines issued by the Center for Disease Control and Prevention in the USA. The diagnosis of DSWI required at least one of the following:

(1) an organism isolated from culture of mediastinal tissue or fluids

(2) evidence of mediastinitis seen during the operation

(3) one of the following conditions: chest pain, sternal instability, or fever (>38° C), in combination with either purulent discharge from the mediastinum or an organism isolated from a blood culture.

4.4 SURGICAL TECHNIQUES (I-IV)

4.4.1 Preoperative prophylactic protocol (I)

In our hospital, the routine preoperative prophylactic protocol included screening for nasal MRSA species with a positive culture indicating a preoperative decolonization protocol for five days. Antiseptic body washing and iodine-impregnated surgical adhesive drapes were used. Prophylactic antibiotic therapy was commenced preoperatively and continued for 48 hours. Intravenous cefuroxime (1.5g every 8 hours) was used if no contraindications existed.

4.4.2 iNPWT (I, IV)

For studies I and IV, an iNPWT device (PICO^{TM}) was installed over a closed wound under sterile conditions in the operating room. It was deemed advisable to maintain enough intact skin between the drains and the wound to achieve an airtight fitting of the dressing. In case of air leakage, additional draping was placed on the ward.

PICO^{TM} was recommended to be used for six to seven days post-operatively. One change of dressing was usually conducted on the ward on the third postoperative day. In study I, nurses were instructed to photograph the wound during dressing change and during removal of the device. In addition, a simple questionnaire was filled in by the nurse when the device was removed.

4.4.3 NPWT (II)

Due to the retrospective nature of this analyses, the use of NPWT was not standardized. All patients had a thorough debridement of all devitalized soft tissue and bone as well as all loose or affected wires. In some patients, sternum was only partially opened.

All patients received antibiotic therapy, initially, with a wide-spectrum antibiotic. Positive microbiological cultures were obtained from all patients and the antibiotic therapy was adjusted accordingly. An infectious disease specialist was frequently consulted. There were no significant changes in the antibiotic treatment protocol during the study period.

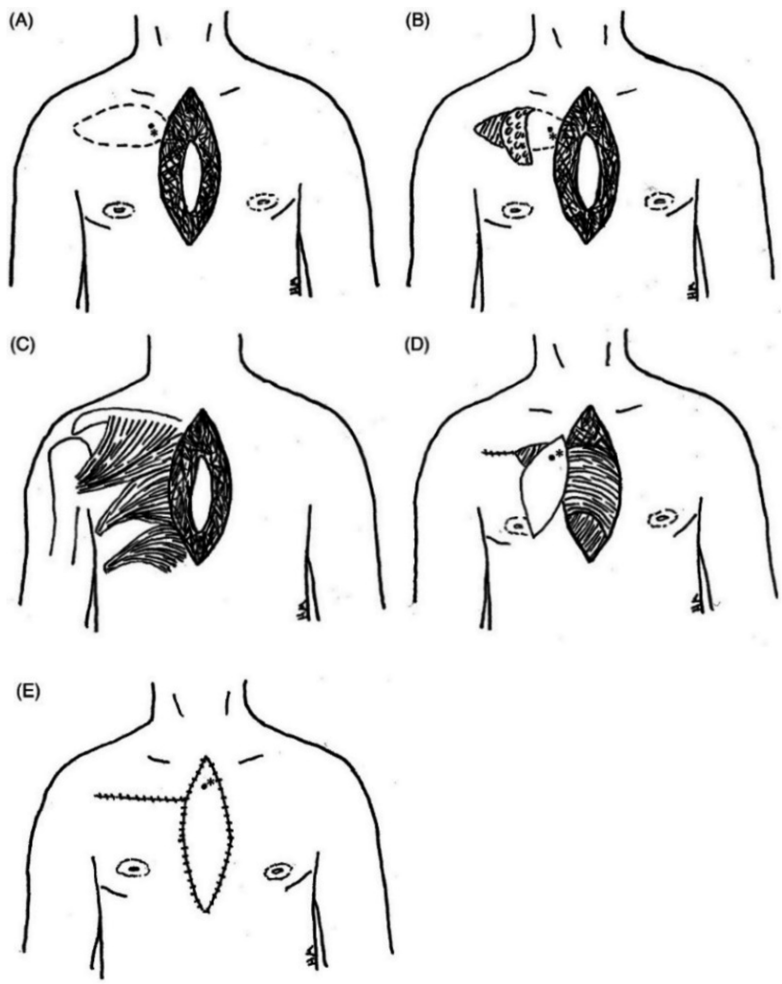
There were several NPWT devices used during the study period. Negative pressure was usually set as -125mmHg but individual judgement was practiced when vulnerable structures were exposed. The dressing material used as a bottom layer varied.

No negative cultures were requested before reconstruction in either group. The timing of the reconstruction was based on clinical judgement. Re-fixation was conducted whenever feasible. Flap reconstruction was used frequently in conjunction with re-fixation and in all patients with a bony deficit or open sternum.

4.4.4 Modified IMAP flap (III)

A preoperative doppler ultrasound assessment was used to locate the perforators (Fig 1A). At least two intact perforators were acquired for this technique. The operation was commenced by raising a horizontally oriented skin flap (Fig 1b). The amount of muscle tissue needed to effectively cover the defect was assessed and a suitable part of the pectoralis major muscle was raised from the thoracic wall. A predetermined part of the muscle was detached from the humerus and mobilized to the level of IMA perforators. Whenever possible, part of the muscle was left intact. The muscle was split, if needed, by the muscle perforators into two or three portions (Fig 1C) which were handled as independent turn-over flaps. The muscle was used to fill the cavity or to cover any bony deficit. Finally, the skin flap was rotated 90 degrees to match the skin defect (Fig 1D).

Figure 1. Technical illustration of the modified IMAP flap operation. (Reprinted by permission from copyright owner; published by Taylor & Francis Group in Scandinavian cardiovascular journal on 04 Jan 2019 available online: https://doi.org/10.1080/14017431.2018.1546897)



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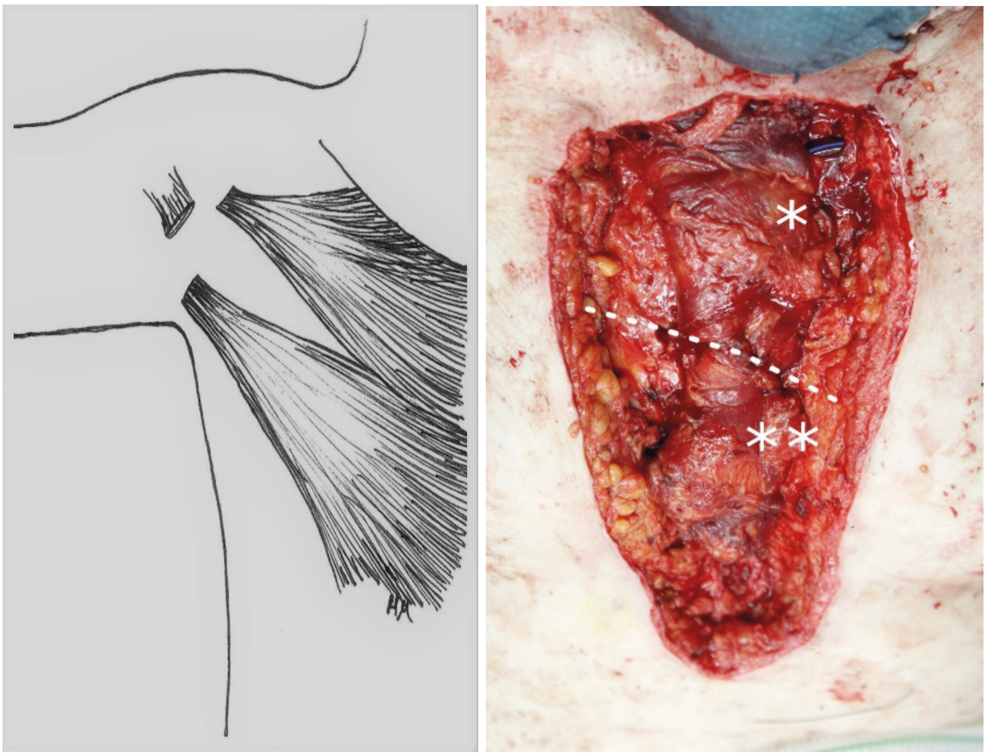
4.4.5 Split pectoralis muscle flap (IV)

The split pectoralis muscle flap was raised with a technique described earlier by Li *et al.* (Li *et al.*, 2004). The muscle was split by the IMA perforators into two or three parts. Muscle portions were handled as turn-over flaps and tailored independently according to individual requirements of the defect.

Figure 2. Schematic drawing of the split pectoralis muscle technique. Split pectoralis major muscle flap with *cranial part and **caudal part combined is sufficient to cover the whole length of sternum. (Reprinted by permission from copyright owner; published by Sage Journals in Scandinavian Journal of Surgery in 2021, available online: https://doi.org/doi:10.1177/14574969211043330)



5 RESULTS

5.1 PREVENTION OF DSWI (I)

It was observed that iNPWT with PICO™ was not effective in preventing sternal wound infections after CABG in high-risk patients. In fact, when compared to conventional sterile wound dressing, PICO™ was associated with slightly higher infection rates. The result remained the same when DSWI (3.9% versus 3.1%), operatively treated superficial wound infections (2.2% versus 0.8%) and all wound infections treated in the university hospital (10.0% versus 7.1%) were considered separately.

Both groups were comparable in terms of patient characteristics and operation derived risk factors (Table 8). After performing a propensity score matched analysis with 174 patients in each group, the results remained the same (Table 9). We also analyzed the incidence of infection in the subgroups of obese (4.3% versus 3.9%, P=0.881), diabetic (5.0% versus 3.8%, P =0.493) and female (4.0% versus 5.1%, P =1.000) patients separately, with no significant differences detected in the infection rates.

We further analyzed the patients that developed DSWI in both groups to discover if infections were more severe in one of the groups, but this was not the case. In the control group, the treatment periods were somewhat longer in the university hospital and in the ICU, but there were more flap reconstructions and more patients that were left with an unstable sternum in the PICO group. In both groups, the most common pathogen causing deep infections was Staphylococcus epidermidis. The mean EuroSCORE II value was higher in the PICO group due to the presence of two patients with exceptionally high values (Table 10).

The treatment had to be interrupted before the fifth postoperative day in 12 (6.7%) patients. The reasons included technical difficulties (n=3) and the patient removing the device because of postoperative delirium or discomfort (n=3). Most of the untimely interruptions were without specified reason. In 12 (6.7%) patients, the duration of the treatment was not determined in the patient records. The remaining 156 (86.8%) patients received iNPWT for five to eight days and the treatment was well tolerated.

Of the seven patients that developed a DSWI in the PICO group, one patient removed the device himself on the fifth postoperative day for some unknown reason, but for the others, the treatment lasted six to seven days with no technical difficulties or adverse effects. There were no signs of infection or irritation of the skin during the removal of the device, and all wounds were considered as closed.

Table 9. Patient characteristics in study I

	Original study groups			**Propensity score matched groups**		
	PICO group n=180	**Control group n=772**	**P value**	**PICO group n=174**	**Control group n=174**	**P value**
Age, mean ± SD	67.0 ± 7.7	68.0 ± 8.6	0.112	70.0 ± 7.8	66.4 ± 8.5	0.798
Female gender	51 (28.5)	196 (25.4)	0.394	50 (28.7)	42 (24.1)	0.331
CABG	138 (77.1)	616 (79.8)	0.715			
CABG + valve	34 (19.0)	156 (20.2)	0.715	34 (19.5)	33 (19.0)	0.892
CABG + composite	5 (2.8)	23 (3.0)	0.922			
UAP	62 (34.6)	260 (33.8)	0.825	60 (34.5)	63 (36.2)	0.737
Diabetes	139 (78.1)	533 (69.6)	0.024	136 (78.1)	130 (74.7)	0.449
Diabetes, type 1	14 (7.8)	48 (6.2)	0.434	14 (8.0)	14 (8.0)	1.000
Kidney disease	16 (8.9)	62 (8.0)	0.706	15 (8.6)	13 (7.5)	0.693
ASO	19 (10.6)	98 (12.7)	0.431	19 (10.9)	22 (12.6)	0.618
Lung disease	32 (17.8)	85 (11.0)	0.013	31 (17.8)	31 (17.8)	1.000
MCI	65 (36.1)	334 (43.3)	0.080	62 (35.6)	62 (35.6)	1.000
Smoking	19 (10.6)	117 (15.2)	0.112	18 (10.3)	15 (8.6)	0.583
BMI	31.6 ± 4.7	32.6 ± 22.8	0.240	31.4 ± 4.8	30.5 ± 5.2	0.209
EuroSCORE II	3.2 ± 4.3	3.8 ± 5.7	0.601	3.2 ± 3.3	2.8 ± 2.2	0.925

Table 10. Infections

	Original study groups			Propensity score matched groups		
	PICO group n=180	**Control group n=772**	**P value**	**PICO group n=174**	**Control group n=174**	**P value**
All infections	18 (10.0)	55 (7.1)	0.192	18 (10.3)	12 (6.9)	0.252
Operatively treated infections	11 (6.1)	30 (3.9)	0.185	11 (6.3)	7 (4.0)	0.333
DSWI	7 (3.9)	24 (3.1)	0.595	7 (4.0)	6 (3.4)	0.777

Table 11. Characteristics of DSWI

	PICO group (n=7)	**Control group (n=24)**
Hospital stay	28.0 ± 10.8	36.7 ± 31.7
ICU stay	3.9 ± 5.6	8.5 ± 9.0
Number of operations	4.57 ± 3.1	5.2 ± 7.8
EuroSCORE II	6.1 ± 5.5	3.18 ± 2.43
Sternum left stabile	4 (57.1)	18 (72.0)
Flap reconstruction	6 (85.7)	17 (68.0)
Staph aureus	1 (14.3)	9 (36.0)
Staph epidermidis	6 (85.7)	12 (48.0)

5.2 TREATMENT OF DSWI (II, III, IV)

5.2.1 Patient characteristics (II, III, IV)

In study II there were no significant differences between the NPWT group or the early muscle flap group in patient derived risk factors, including age, gender, BMI, and co-morbidities (Table 12). Furthermore, operation derived risk factors, such as type of the original cardiac surgery, urgency of the operation, and perfusion time, were equally distributed as well (Table 14). The EuroSCORE II value was somewhat higher in the early muscle flap group but with no statistically significant difference. The characteristics in the subgroup of modified IMAP flap reconstruction are included in Tables 12 and 14.

All groups in study IV were also comparable when evaluating pre- and postoperative characteristics (Tables 13 and 15).

Table 12. Patient characteristics and co-morbidities in studies II and III

	NPWT group n=55	**Early muscle flap group n=60**	**IMAP group n=10**
Female	20 (36.4)	35 (63.6)	5 (50.0)
Male	20 (33.3)	40 (66.7)	5 (50.0)
Age	67.9 ± 9.7	67.5 ± 10.1	71.8 ± 10.7
BMI	30.6 ± 5.6	30.0 ± 5.5	34.2 ± 5.8
EuroSCORE II	3.4 ± 2.3	4.83 ± 6.6	-
Diabetes	33 (60.0)	28 (46.7)	5 (50.0)
Diabetes, type 1	4 (7.3)	5 (8.3)	0
Kidney disease	8 (14.3)	6 (10.0)	1 (10.0)
Heart failure	11 (20.0)	11(18.3)	0
Peripheral artery disease	7 (12.7)	11 (18.3)	0
Chronic pulmonary disease	11 (20.0)	13 (21.7)	4 (40.0)
Previous myocardial infarction	23 (41.8)	24 (40.0)	4 (40.0)
Smoking	8 (14.5)	12 (20.0)	1 (10.0)
Immunosuppression	4 (7.3)	3 (5.0)	0

Table 13. Patient characteristics and co-morbidities in study IV

	Pectoralis with prior NPWT and iNPWT	**Pectoralis without NPWT**	**Pectoralis with prior NPWT only**
Female	15 (62.5)	29 (60.4)	8 (80.0)
Male	9 (37.5)	19 (39.6)	2 (20.0)
Age	71.1 ± 9.5	67.0 ± 9.3	69.4 ± 7.0
BMI	29.8 ± 5.4	30.2 ± 5.8	30.6 ± 4.3
EuroSCORE II	4.2 ± 3.4	3.9 ± 3.9	3.8 ± 2.2
Diabetes	12 (50.0)	25 (52.1)	5 (50.0)
Diabetes, type 1	12 (50.0)	25 (52.1)	5 (50.0)
Kidney disease	3 (12.5)	4 (8.3)	2 (20.0)
Heart failure	3 (12.5)	10 (20.8)	2 (20.0)
Peripheral artery disease	3 (12.5)	5 (10.4)	1 (10.0)
Chronic pulmonary disease	7 (29.2)	9 (18.8)	2 (20.0)
Previous myocardial infarction	14 (58.3)	20 (41.7)	5 (50.0)
Smoking	3 (12.5)	6 (12.5)	5 (50.0)

Table 14. Operation derived risk factors in studies II and III

	NPWT group	**Control group**	**IMAP flap**
CABG	40 (72.6)	52 (86.7)	8 (80.0)
CABG + valve	9 (16.4)	6 (10.0)	2 (20.0)
Valve	5 (9.1)	1 (1.7)	-
Aorta	1 (1.8)	1 (1.7)	-
Elective	23 (41.8)	28 (46.7)	2 (20.0)
Urgent	25 (45.5)	27 (45.0)	4 (40.0)
Emergency	7 (12.7)	5 (8.3)	3 (30.0)
Re-sternotomy	6 (10.9)	5 (8.3)	1 (10.0)
Perfusion time	106.9 ± 90.0	110.5 ± 49.0	-
Blood transfusion	2.4 ± 2.4	2.7 ± 3.4	-

Table 15. Prior cardiac operations in study IV

	Pectoralis with prior NPWT and iNPWT	**Pectoralis without NPWT**	**Pectoralis with prior NPWT only**
CABG	14 (58.3)	42 (87.5)	7 (70.0)
CABG + valve	4 (16.7)	4 (8.3)	2 (20.0)
Aorta	3 (12.5)	1 (2.1)	1 (10.0)

5.2.2 Pathogens and classification of infections (II)

The pathogens were comparable between the groups of NPWT and early muscle flap reconstruction (Table 16). Staphlylococcus epidermidis was the most common cause of DSWI in both groups whereas MRSA was very rare in our material.

Table 16. Distribution of pathogens in study II

Pathogens	NPWT group n=55	Control group n=60
Staphylococcus (all species)	49 (89.1)	54 (90.0)
Staphylococcus epidermidis	26 (47.3)	32 (53.3)
Staphylococcus aureus	20 (36.4)	19 (31.7)
Propionbacter acnus	1 (1.8)	3 (5.0)
Enterococcus	2 (3.6)	-
Pseudomonas aeruginosa	1 (1.8)	1 (1.7)
Staphylococcus capitis	1 (1.8)	1 (1.7)
MRSA	-	1 (3.3)
Bacillus cereus	1 (1.8)	-
Staphylococcus haemolyticus	1 (1.8)	-
Staphylococcus species	1 (1.8)	-
Staphylococcus viridans	-	1 (1.7)
Klebsiella	-	1 (1.7)
Missing information	1 (1.8)	-

In study II, DSWI presented 18 ± 13.3 days after initial sternotomy. The patients were classified according to the criteria described by El Oakley and Wright (El Oakley and Wright, 1996), with no significant difference between the groups (Table 17). DSWI presenting within two weeks after operation in the absence of risk factors represents Type I in that classification. Type II includes DSWI presenting at two to six weeks after operation in the absence of risk factors. Type IIIA refers to DSWI type I in the presence of one or more risk factors (including diabetes and obesity) and Type IIIB as DSWI type II in the presence of one or more risk factors. Type V includes DSWI presenting for the first time more than six weeks after operation.

Table 17. El Oakley classification in study II

	NPWT group n=55	**Control group n=60**
Type I	2 (3.6)	4 (6.7)
Type II	10 (18.2)	12 (20)
Type IIIA	20 (36.4)	24 (40)
Type IIIB	20 (36.4)	18 (30)
Type V	3 (5.5)	1 (1.7)
Missing information	-	1 (1.7)

5.2.3 NPWT (II)

All-cause in-hospital mortality was 14.5% (*n*=8) in the NPWT group and 0% in the early muscle flap group, a difference that was statistically significant (*P*=0.002). With seven patients, the cause of death was related to DSWI with additional liver, kidney and / or respiratory failure. One patient suffered a massive stroke. Three patients had had a flap reconstruction before death, two had undergone a direct closure and three had still an open wound. One of the patients who died after reconstruction had a modified IMAP flap reconstruction. Death occurred a median of 34 (5-127) days after diagnosis of the DSWI.

In the NPWT group, there were longer treatment periods in the ICU as well as in the university hospital, more visits to the operating room, a longer delay from diagnosis of DSWI to reconstruction and a higher mortality. All these differences were statistically significant (Table 18).

Table 18. The most relevant differences between the NPWT group and the early muscle flap group detected in study II

	NPWT group	**Early muscle flap group**	**P value**
Treatment in ICU	10.5 ± 13.4	6.9 ± 17.7	0.028
Length of hospitalization (university hospital)	36.8 ± 28.1	25.6 ± 38.7	<0.001
Number of operations	4.5 ± 6.0	1.4 ± 0,9	<0.001
Delay from diagnosis to reconstruction	23.5 ± 33.2	4.66 ± 12.1	<0.001
Deaths	8 (14.5)	0	0.002

NPWT was initiated 2.8 ± 4.3 days after the diagnosis of DSWI. The length of NPWT was 22.7 ± 31.6 days. More than one period of NPWT before reconstruction was needed in 9.0% (*n*=5) of the patients. We analyzed separately the 16 (29.1%) patients in whom the NPWT lasted for more than 21 days but no additional increase in surgical complications or deaths was found in this subgroup.

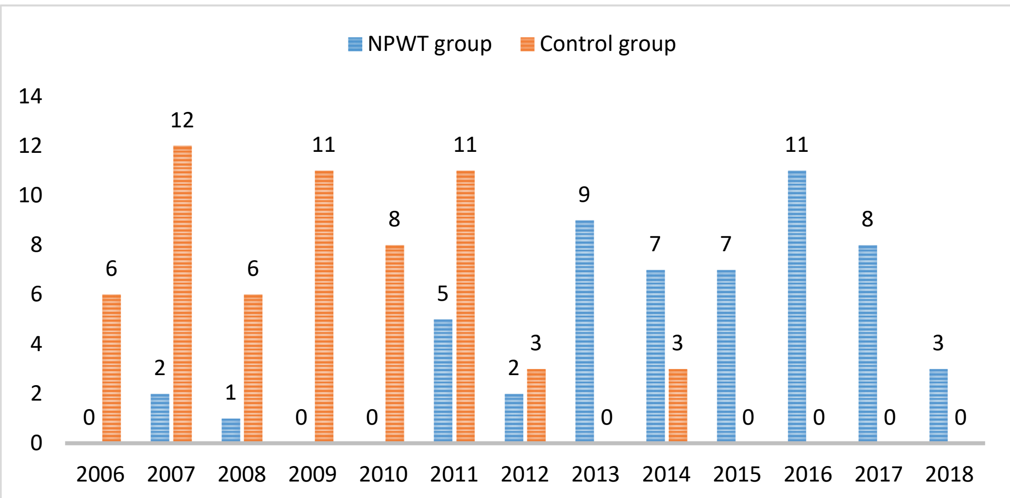
There was a slightly higher number of positive blood cultures and somewhat more elevated CRP levels at the time of the first debridement in the NPWT group. In the NPWT group the CRP levels continued to rise after the debridement leading to significantly higher overall CRP levels. In the early muscle flap group, however, the CRP levels declined after the flap reconstruction (Table 19). On average, reconstruction was carried out 4.66 ± 12.1 days after the diagnosis.

Table 19. Incidence of bacteremia and CRP levels.

		NPWT group	**Early muscle flap group**	**P-value**
Bacteremia, *n* (%)	Before debridement	18 (32.7)	12 (20.0)	0.140
	During treatment	23 (41.8)	17 (28.3)	0.170
Highest CRP, mean ± SD	Before debridement	191.8 ± 122.0	152.5 ± 105.1	0.090
	During treatment	279.0 ± 108.3	228.6 ± 78.5	0.012

In our hospital, NPWT became the first line treatment option of DSWI in the year 2011 (Figure 3). There were three patients treated with NPWT before 2011 and six patients treated with early muscle flap reconstruction after 2011.

Figure 3. The introduction of the NPWT in our hospital.



There were 62 patients in whom NPWT was used either as a first line treatment choice (*n*=55) or only after an unsuccessful flap reconstruction (*n*=7). Five (8.0%) of these patients had an NPWT associated bleeding complication and underwent an emergency operation. The bleedings occurred at a median of 5 (2-8) days after the initiation of the NPWT. One bleeding occurred from the right ventricle and another from a ruptured graft but the other three were from granulation tissue or from an undetermined source. There was no mortality associated with bleeding.

Three of the patients had white gauze and two of the patients had nanocrystalline silver as the first layer to cover the heart to prevent ruptures. Unfortunately, the pressure of NPWT of these patients was left unresolved.

NPWT was discontinued before sternal closure either temporary or permanently in 15 patients. The reasons for discontinuation concerning the first effort of treatment are specified in Table 20.

Table 20. Reasons for discontinuation of NPWT (un-published)

	NPWT group n=55
Closure	38 (69.1)
Bleeding	2 (3.6)
Infection	5 (9.1)
Chronic osteitis	2 (3.6)
Necrosis	1 (1.8)
Transfer to local wound care	2 (3.6)
Missing info	2 (3.6)
Death	3 (5.5)

Flap reconstruction was performed in 72.7% (n=40) of the patients in the NPWT group. The need for distant flaps was slightly decreased as compared to the early muscle flap group but the difference was not statistically significant. It should be noted that the ten patients treated with re-fixation and direct closure without

NPWT or muscle flaps were excluded from the analysis. Reconstructive methods are listed in more detail in Table 21.

Table 21. Reconstruction methods

		NPWT group n=55	**Early muscle flap group n=60**
Local flaps		34 (61.8)	50 (83.4)
	Pectoralis advancement	2 (3.6)	6 (10.0)
	Pectoralis turnover	2 (3.6)	8 (13.3)
	Turn over + advancement	-	1 (1.7)
	Split pectoralis	20 (36.4)	35 (58.3)
	IMAP + pectoralis	10 (18.2)	-
Distant flap		6 (10.9)	10 (16.6)
	Omentum	3 (5.5)	2 (3.3)
	Latissimus dorsi	2 (3.6)	2 (3.3)
	Rectus abdominis	1 (1.8)	6 (10.0)
Others		15 (27.3)	
	Skin graft	3 (5.5)	-
	Direct closure	4 (7.3)	-
	Secondary closure	3 (5.5)	-
	Death before closure	5 (9.1)	-

5.2.5 Sternal re-fixation (II)

The sternal fixation was stabile (re-fixated, plated, or not fully opened) in 63.7% (*n*=35) of the patients in the NPWT group and in 88.4% (*n*=43) of the patients in the early muscle flap group. The sternum was totally removed or otherwise left without re-fixation in 36.3% (*n*=15) of the patients in the NPWT group and 10.0% (*n*=6) of the patients in the early muscle flap group. The difference in sternal stability between the groups was statistically significant (*P*=0.001).

Of the ten patients that had undergone IMAP flap reconstruction, three patients achieved re-fixation, two patients underwent partial re-fixation, four patients were left with open sternum, and in one patient, total sternectomy was required.

Table 22. Management of the sternum in studies II and III

	NPWT group n=55	**Early muscle flap group n=60**	**IMAP flap n=10**
Re-fixated	21 (38.2)	45 (75.0)	5
Plated	1 (1.8)	1 (1.7)	-
Left open or removed	20 (36.3)	6 (10.0)	5
Not fully opened	13 (23.6)	7 (11.7)	-
Missing information	-	1 (1.7)	-

5.2.6 Modified IMAP flap (III)

In ten patients, the reconstruction was conducted with a modified IMAP flap. The muscle portion of the flap included one third to two thirds of the muscle, sometimes divided into two separate sections. In two patients, the entire right side of the pectoralis major muscle was used. No other flaps including the left pectoralis major muscle flap were needed. The mean duration of the operation was 95 minutes including possible debridement and re-fixation.

5.2.7 Surgical complications after flap reconstruction (II, III, IV)

NPWT was associated with fewer surgical complications in study II. There were somewhat fewer surgical complications as well as complications needing operative treatment in the NPWT group compared to the early muscle flap group (45% versus 60%, *P*=0.137; 13% versus 18%, *P* =0.530, respectively). NPWT was used after a flap-related complication in 20.0% (*n*=11) patients in the NPWT group and in 11.7% (*n*=7) patients in the early muscle flap group. The complications observed in study II are further described in Table 23.

The complication rates in the subgroup of modified IMAP flap were comparable to those encountered in other reconstructions. The major complications in this subgroup included a donor-site hematoma and a partial necrosis of the tip of the flap needing a small skin graft (Table 23). The most severe complication was a persistent infection that required multiple operations before a full recovery within one year. During that time, the IMAP flap itself stayed vital. There were no flap losses.

Split pectoralis major muscle flap was associated with less complications in our material compared to other forms of pectoralis major muscle flap reconstruction.

The complication rate after pectoralis major muscle flap reconstruction decreased from 50% to 33% when both preoperative NPWT and iNPWT after reconstruction were used (*P* =0.180). Major complications needing operative treatment declined from 29.2% to 12.5% (*P* =0.148). The need for an additional flap decreased from 14.6% to 4.2% (*P*=0.255). The greatest reduction occurred in the number of bleeding complications and partial flap necrosis, although the groups were too small to draw any definitive conclusions (Table 24). The complication rates after pectoralis major muscle flap in the second control group with preoperative NPWT only were in between the numbers represented above.

In addition to reduced complication rates, iNPWT after flap reconstruction was associated with a decreased length of hospital stay and a shorter length of stay in the ICU after flap reconstruction but the differences were not statistically significant.

Rates of surgical complications in different study settings are further described in Table 25.

Table 23. Surgical complications observed in study II

	NPWT group n=55	Control group n=60	IMAP group n=10
Skin dehiscence	10 (18.2)	11 (18.3)	1 (10.0)
Bleeding	5 (9.1)	10 (16.7)	2 (20.0)
Partial necrosis	7 (12.7)	18 (30.0)	3 (30.0)
Infection	8 (14.5)	4 (6.7)	1 (10.0)
Fistula	4 (7.3)	4 (6.7)	-
Herniation	-	1 (1.7)	-

Table 24. Surgical complications observed in study IV

	Pectoralis with prior NPWT and iNPWT n=24	Pectoralis without NPWT n=48	Pectoralis with prior NPWT only n=10
Skin dehiscence	4 (16.7)	7 (14.6)	1 (10.0)
Bleeding	1 (4.2)	8 (16.7)	2 (20.0)
Partial necrosis	3 (12.5)	13 (27.1)	1 (10.0)
Infection	1 (4.2)	3 (6.3)	2 (20.0)
Fistula	-	3 (6.3)	1 (10.0)

Table 25. Surgical complications encountered in studies II-IV

	N	All complications	Major complication	Need for an additional flap
NPWT versus early muscle flaps				
NPWT group	55	25 (45.5)	13 (23.6)	5 (9.1)
Early muscle flap group	60	36 (60.0)	18 (30.0)	6 (10)
Pectoralis muscle flaps with or without NPWT				
All pectoralis flaps without NPWT / iNPWT	48	24 (50.0)	14 (29.2)	7 (14.6)
All pectoralis flaps with prior NPWT	10	4 (40.0)	2 (20.0)	1 (10.0)
All pectoralis flaps with NPWT and iNPWT	24	8 (33.3)	3 (12.5)	1 (4.2)
Different forms of pectoralis muscle flap				
Modified IMAP flap	10	7 (70.0)	3 (30.0)	1 (10.0)
Split pectoralis flap	58	22 (37.9)	10 (17.2)	5 (8.9)
Other forms of pectoralis major flap	20	14 (70.0)	11 (55.0)	5 (25.0)

6 DISCUSSION

NPWT has revolutionized the wound care and gained rapidly an established position in the treatment of open wounds, including the sternal wounds after DSWI. In addition, a growing number of publications support the use of iNPWT in the prevention of wound complications of closed surgical wounds, including a median sternotomy wound in open-heart surgery. Lately, a few reports of the application of iNPWT after flap reconstruction to prevent surgical complications have been published.

However, there are several shortcomings with the published research. The aspect of low-quality evidence and the presence of bias have been addressed in meta-analyses and systematic reviews concerning both NPWT and iNPWT (Ingargiola, Daniali and Lee, 2013; Semsarzadeh *et al.*, 2015; De Vries *et al.*, 2016; White, Meyer and Harlin, 2019). The original articles may have contained multiple confounding factors, clinical heterogeneity, and small study groups. Another concern is the presence of sponsorship from the manufacturer of the devices (Kairinos *et al.*, 2014). In addition, publication bias may affect the results, especially concerning observational studies, since positive results may be more likely published than their negative counterparts (Peinemann and Labeit, 2019). Attention has been drawn to the varying quality of studies reporting the use of NPWT. This does not only concern sternal wounds, but the use of NPWT in general (Othman, 2012; Peinemann and Labeit, 2019).

Our studies share some of these problems, including relatively small patient groups and some potential confounding factors because of the non-randomized study design. We took efforts to control these confounding factors, for example by conducting a propensity score matched analysis in study I. The device manufacturers were not involved in our studies. Most of our results could be labelled as negative. However, since we evaluated treatments that were already in widespread use, reporting these results was considered as clinically highly important.

6.1 INPWT IN THE PREVENTION OF STERNAL WOUND COMPLICATIONS (I, IV)

In contrast with previous studies, we did not find any benefit in using iNPWT to prevent DSWI. There are several possible explanations for this discrepancy. First, the infection rate in our control group was very low. The rate of DSWI in this group of high-risk patients treated with conventional wound care was 3.1%. This was considerably lower compared to, for example, the rate of 16% of obese patients with operatively treated sternal infection in the study of Grauhan *et al.*, or the 11% rate of DSWI in high-risk patient group in the study of Tabley *et al.* (Grauhan *et al.*, 2013; Tabley *et al.*, 2020). These examples represent previously published studies concerning the effect of iNPWT to prevent sternal wound complications.

There are some shortcomings in the previous studies. In some studies the rate of deep infections was not specified separately (Grauhan *et al.*, 2014) or not diagnosed in either groups (Witt-Majchrzak, Zelazny and Snarska, 2015). In addition, some studies have been manufacturer-sponsored (Colli, 2011; Grauhan *et al.*, 2014; Nherera *et al.*, 2018; Tabley *et al.*, 2020). Only two of the studies have concentrated on PICO™ (Witt-Majchrzak, Zelazny and Snarska, 2015; Tabley *et al.*, 2020).

The relatively small size of our study group could have meant that we failed to detect a decline in the infection rates considering the low incidence of infections in the beginning of the study. However, it has been observed in the previous studies with high-risk patients that every two out of three or three out of four infections could have been prevented with iNPWT (Grauhan *et al.*, 2013; Tabley *et al.*, 2020). As a consequence, it seems more than likely that we would have detected a tendency towards fewer infections had this been present in our 180 high-risk patients.

PICO™ was introduced into clinical practice in our hospital after experimenting on different systems including Prevena™. PICO™ was considered more economical and easier to use. During the study period, the cost of PICO™ was less than half of the cost of Prevena™. Our results, which indicated no benefit of using PICO™ to prevent DSWI, are in contradiction with the previous results from studies utilizing mainly Prevena™. In addition, when used after sternal flap reconstruction, the decrease in complication rates with PICO™ was less than the decrease reported in studies utilizing Prevena™. In our study, the rate of major flap related complications in the PICO group declined to 12.5%, compared to 5.3-3% in previous studies (Lo Torto et al., 2017; Nickl et al., 2018).

It might be, however, too early to draw the conclusion that PICO™ is an inferior system. The superiority of one system over another has not been proved in comparative studies. There is one meta-analysis concentrating that topic: it concludes that considerable better results could be achieved with Prevena™ than with PICO™ (Singh *et al.*, 2019). However, the meta-analysis, financed by the manufacturer of Prevena™, had several limitations, including significant clinical heterogeneity. Nonetheless, with long or multiform skin incisions, Prevena™ has the benefit of allowing more individual tailoring and fitting of the wound dressing. On another hand, depending on the size of the dressing used, PICO™ is able to stabilize a larger area of skin around the wound, with a kind of splinting effect. This could be potentially helpful in the early mobilization of the patient.

According to prior studies, it seems that iNPWT could decrease the rate of infections, especially those caused by gram positive bacteria (Grauhan *et al.*, 2013). Our results did not confirm this proposal. We found Staphylococcus epidermidis to be the most common bacteria to cause DSWI irrespective of the form of postoperative wound care. The spread of normal skin flora to the sterile operation field already intraoperatively has been demonstrated and can explain the results (Kühme, Isaksson and Dahlin, 2007).

EuroSCORE II is a scoring system developed to evaluate mortality related to cardiac surgery. Cayci *et al.* demonstrated that higher EuroSCORE values were also associated with an increased risk of infection (Cayci *et al.*, 2008). In the iNPWT group, there were a few patients with very high EuroSCORE II values. Most likely, it would not have been possible to prevent infections in these patients with any method.

The use of iNPWT after sternotomy was increasing in our hospital before the initiation of this study. As a consequence, 25 high-risk patients were excluded from the control group since those patients had been already treated with iNPWT. In addition, a non-randomized study protocol carries an inherent risk of potential selection bias. For these reasons, we used propensity score matching to control for the confounding factors.

Based on clinical judgement, iNPWT was considered most useful in female patients with large breasts. The movement of the breasts may cause excess mechanical stress to the wound. However, when analyzing female patients separately, we did not find evidence to support this hypothesis. An elastic bandage was utilized with all female patients in both groups to control lateral tension from the breasts.

We encountered some minor technical difficulties during the study protocol. More difficulties were noted in patients that were transferred to other wards with less surgically oriented nursing staff. This indicates that there is a slight learning curve with the device. No significant adverse effects were noted. None of the infections were associated with early discontinuations of the treatment.

It is interesting, that while iNPWT was considered ineffective in the prevention of DSWI, a decrease in wound complications after sternal flap reconstruction was noticed with its use. It could be speculated that iNPWT is more effective when used on high-risk wounds with relatively high overall complication rates. Similarly, iNPWT has seemed to be more beneficial in the prevention of DSWI in previous studies, in which the overall rate of wound infections remained relatively high.

6.2 TREATMENT OF DSWI (II, III, IV)

6.2.1 NPWT – a critical appraisal

After years of almost uniformly positive reports of using NPWT, more critical comments have appeared during the last two years. A systematic review prepared by White *et al.* in 2019 questioned the effectiveness of NPWT as a bridge to reconstruction (White, Meyer and Harlin, 2019). In 2020, two comparative studies considered NPWT as an inferior method compared with early reconstruction (Pan *et al.*, 2020; Hämäläinen *et al.*, 2021). Previously, critical approaches to NPWT have been few. The meta-analysis conducted by Falagas *et al.* in 2013, even though reporting positive results with NPWT, demanded confirmation of the reduced mortality in multivariate analysis and more rigorous reporting of the complications (Falagas *et al.*, 2013). A literature review from Raja *et al.* in 2007 recommended an initiation of a randomized controlled trial to validate the effectiveness of NPWT in the treatment of DSWI (Raja and Berg, 2007). No such randomized studies have been conducted.

In our study, NPWT was associated with higher mortality and higher costs, as a consequence of longer treatment periods in the university hospital and in the ICU, as well as a greater number of operations. These results were in contrast with most reports in the literature. However, similar results have been published by Pan *et al.* and Hämäläinen *et al.* in 2020, both comparing NPWT with early reconstruction (Pan *et al.*, 2020; Hämäläinen *et al.*, 2021). It seems that the NPWT may be superior compared to conventional treatments, such as closed irrigation, open daily irrigation, and open packing, but not necessarily superior to early flap reconstruction.

It appears that the use of NPWT has gained rapid and widespread acceptance as a first line option in the treatment of DSWI, and in other indications as well, even though the compiled evidence from previous studies seems limited. One can speculate the reasons for this rapid change in clinical practice. The technique is familiar to surgeons from other indications, and the benefits seem apparent at a first glimpse. As described by Sjögren *et al.*, there does not seem to be a learning curve and the technique is easy to adapt (Sjögren *et al.*, 2008). Patients can be mobilized with NPWT, and they can even be sent to local hospitals or home with the device. The potentially difficult choice of final reconstruction can be easily postponed. As Bain *et al. s*tated, it can be appealing to “try VAC first” instead of the early combined cardiothoracic and plastic surgery approach (Bain, Lo and Soldin, 2012). In some institutions, consulting plastic surgeons may even require referring the patient to another hospital. Lindsey *et al.* also speculated that since the DSWI is, fortunately, a relatively rare complication, the personal experience of a single surgeon tends to remain limited (Lindsey, 2002). This may complicate the decision making.

In our material the use of NPWT was connected to a delay of reconstruction. In our opinion, this was the most notable factor explaining the inferior results in the NPWT group. In their study, Karra *et al.* described that a delay greater than three days between the debridement and sternal closure tended to increase the one-year mortality by more than six-fold (Karra *et al.*, 2006). A deterioration in patients’ nutritional status and general condition may be a consequence of prolonged wound treatment.

Subsequently, we searched for other possible factors which would explain the inferior results in the NPWT group but found no convincing answers. There was no significant difference in the comorbidities between the two groups. In fact, EuroSCORE II values were slightly higher in the control group. The types of infection according to El Oakley classification were similarly distributed between the two groups. In the NPWT group, there were slightly more positive blood cultures as well as somewhat higher CRP levels at the time of the first debridement, but without statistical significance. However, in the NPWT group, the CRP levels continued to rise after the debridement, and this led to significantly higher overall CRP levels. The early flap reconstruction within a few days after the diagnosis led to a faster decline in the CRP levels.

Another significant finding was the decreased number of re-fixations in the NPWT group. The delayed reconstruction may also be the most important reason for the decreased number of re-fixations. In some patients, the re-fixation was not possible because of the poor quality of the sternal bone after prolonged infection or repeated debridement. In addition, with the longer use of NPWT the remnants of sternum might have become fixated to the bottom of the wound and to the heart, causing difficulties in re-fixation. The risk of ventricular rupture may be linked with this process (Davison *et al.*, 2007; Reiss *et al.*, 2007).

There have been some attempts to resolve this problem. Thermo-reactive nitinol clips have been recommended to close the sternum without damaging the heart. These clips can be inserted without any preparation of substernal tissue (Tocco *et al.*, 2009). Salica *et al.* have tackled this issue by placing interrupted wires only in the anterior surface of the sternum (Salica *et al.*, 2014). Authors stated that the above-mentioned fibrotic growth in substernal tissues contributed to a stable osteosynthesis by itself. The same principle has been mentioned in other studies as well.

In our study, the patients in each group were operated during different time periods although with a short overlap. Patients in the NPWT group were operated later and would therefore be expected to have better outcomes. In 2011, NPWT had become considered as the golden standard of treatment. However, there were some differences in the adoption of the new treatment between different surgeons. Figure 3 illustrates the patients in the two groups in a timeline and indicates that selection bias cannot explain the results from this study.

It is also notable, that the results in the control group, using early muscle flap closure, with zero mortality, were exceptionally good (Berg and Jaakkola, 2013).

There were more bleeding complications in our study compared to previous reports. However, fortunately, most of those were from the granulation tissue and we did not encounter any mortality related to bleeding. It should be remembered that bleeding complications after DSWI are not associated only with the use of NPWT but have been encountered also with conventional treatment methods. The risk of bleeding is related to the infection itself and the movement of the sternal edges. Therefore, it could be speculated that an early muscle flap closure would be the most beneficial approach to prevent this complication. In our study, it seems that the patients who suffered from a bleeding even had a distinctly difficult infection associated with other complications as well. Nonetheless, because of the small number of patients, statistical analysis was not possible.

There are other complications and downsides to NPWT that are rarely considered. In our study material, there were several unplanned interruptions of the treatment because of, for example, infectious relapse. Pain, mostly related to dressing changes, and skin irritation, are other factors to be considered.

6.2.2 Modified IMAP flap and split pectoralis major muscle flap

There were more distant flaps used in the early muscle flap closure group compared to the NPWT group. During the study period, in 2010, there was a new local flap reconstruction method introduced in our hospital combining split pectoralis major muscle flap with an IMAP flap. With this technique, it was possible to replace some distant flaps with a local option. The introduction of this method can partly explain the decline in the need of distant flaps seen in the NPWT group.

All the DSWI patients treated with the modified IMAP flap in this study had the wound preconditioned with NPWT. It could be speculated that an introduction of an IMAP flap offered a solution for the problems that were associated with the wider use of NPWT. Earlier, with one-stage reconstruction, the direct skin closure was more often possible. With the delay attributable to the NPWT, the skin edges showed a tendency to withdraw. The defect was also exposed to further widening after repeated debridement. In the worst-case scenario, the nutritional status and general condition of the patient declined after prolonged treatment, and this led to exclusion of some of the more demanding reconstructive options.

In our hospital, the IMAP flap did not replace pectoralis major muscle flap as a first-line option in sternal reconstruction. The IMAP flap was mostly used with the kinds of defects that comprised the whole length of sternum and were too wide to allow direct skin closure. It was used instead of skin grafts and distant flaps, such as rectus abdominis, omentum, or LD.

The benefits include the reduction in donor-site morbidity and the possibility to preserve muscle function since part of the muscle was usually left intact. The operation time was very brief in our series operated exclusively by an experienced senior plastic surgeon. The dissection of the flap is relatively straightforward. The independent arrangement of the muscle and skin flaps allows tailored reconstruction in various defects. Combining the IMAP flap with split pectoralis major muscle flap provides more vascularized tissue compared to plain fasciocutaneous reconstruction. This could be beneficial in deeper defects, in case of bony deficits, and osteomyelitis.

The bilateral use of IMA in the primary cardiac procedure is considered as a contraindication. A visible scar at the donor site and breast asymmetry in female patients are disadvantages of this technique. In our elderly and multimorbid study population these were highly accepted downsides. Postoperative asymmetry of the breast was treated with brassiere selection.

In our hospital, the split turn-over pectoralis major muscle flap reconstruction was the most common reconstructive method used in the treatment of DSWI during the study period. In this technique, the muscle is split into two or three parts based on IMAP and handled as independent turn-over flaps. With this technique, in contrast to the muscle-sparing split technique described with modified IMAP flap, the whole muscle is most often used in the reconstruction. The technique has been previously described by Li *et al.* (Li *et al.*, 2004).

The technique is preferred because of the ability to tailor muscle portions according to individual requirements. Its reach into the most caudal part of the sternum is superior when compared to advancement or a standard turn-over flap design. Split pectoralis muscle flap remains, according to the literature, less widely exploited than other modifications of the pectoralis major muscle flap. Although fast and straight-forward in experienced hands, the technique is slightly more technically demanding compared to advancement flaps and standard turn-over flaps. As far as we are aware, the present work describes the largest patient series utilizing this technique.

The complication rates with split pectoralis major muscle flap seem somewhat lower than with other forms of pectoralis major muscle flap. However, a selection bias may have affected the results.

During the study period, multiple other forms of pectoralis major muscle flap, including unilateral and bilateral turn-over and advancement flaps, combined advancement and turn-over flaps, and some of the above-mentioned flaps covered with skin grafts, were used as well. The wide choice of flaps reflects the co-operation between cardiothoracic and plastic surgeons in our hospital during the study period. The size and location of the defect, the ability to achieve direct closure of the skin, the existence of intact IMA, and the experience of the surgeon were some of the factors that influenced the choice of flap.

6.2.3 Surgical complications after reconstruction

This is a multimorbid group of patients with serious infections. The complication rate was high in all patient groups in these study materials, irrespective of the closure method. The complication rates depicted in earlier investigations have ranged between 25.3–55.6%. However, it should be noted that most of these surgical complications were minor and flap losses are extremely rare.

There were fewer surgical complications in the NPWT group than in the early muscle flap group. The higher number of deaths in the NPWT group can explain a small part of this difference. The preconditioning of the wound may be beneficial in terms of surgical complications despite the other considered disadvantages of delayed closure. The gradual introduction of iNPWT with flap reconstructions should be considered as a confounding factor in study II.

There was a slightly higher complication rate in the subgroup of modified IMAP flap closure compared to other reconstruction methods. This is partly explained by the fact that these patients represent a more difficult form of infection compared to, for example, patients with a simple pectoralis major muscle reconstruction.

From the results obtained in study IV, we concluded that the rate of surgical complications could be decreased by using iNPWT. However, it seems that some of the decrease in the complication rate may be due to preconditioning of the wound with NPWT, as discussed earlier. Prior studies concerning the use of iNPWT after flap reconstruction either have encountered this same confounding factor or have not discussed the matter at all. All studies published concerning the use of iNPWT after flap reconstruction have had small study groups, ours included, and thus the results must be viewed as preliminary.

Interestingly, a decrease in hospitalization length after flap reconstruction was associated with iNPWT. The same did not apply to the group of preoperative NPWT only. Earlier mobilization with iNPWT stabilizing the wound may explain the results. If verified in future studies, the decrease in the duration of hospitalization would mean that iNPWT could be regarded as highly cost-effective in this indication.

Eight out of ten patients with IMAP flap had iNPWT after reconstruction. We did not encounter any dehiscence of the donor site, described previously with the use of IMAP flap in sternal reconstruction. It can be speculated, that iNPWT may have exerted a beneficial effect, although the material is far too small to draw any definite conclusions.

6.3 STRENGTHS AND LIMITATIONS

The main limitations of these studies relate to the study protocol and relatively small patient groups. We conducted two retrospective comparative studies, described two patient series, and conducted a prospective study with a historical control group and a propensity score analysis. However, in this study field randomized trials are rare, and considering the treatment of DSWI, non-existent.

When considering the prospective study design, since iNPWT was already being used in our hospital and considered beneficial at the time, we did not want to deny it to the high-risk patients simply to achieve randomization. For this reason, we included all high-risk patients in the study group and used historical controls. However, the size of the study group is relatively large in comparison with previous studies, and the fact that we conducted a propensity score analysis is considered as an advantage.

All the data was collected solely from the charts of the university hospital. Some minor late complications may have been treated in local hospitals. However, neither sternal reconstructions nor open-heart surgery are performed in any of these hospitals. Any relevant complications would have been referred to our hospital for treatment. This applies to all patient groups and is therefore unlikely to have influenced the results in comparative studies.

Most of the data was collected from patient records. The quality of these records in Finland is of a good standard. There was very little missing data throughout the study. All the data was collected solely by the author meaning that it is uniform. The author has not been involved in decision making in the treatment of any of these patients and is therefore unbiased. All the infection rates are based on manually collected information that reliably reflects the real incidence of these events.

6.4 FUTURE ASPECTS

The central role of NPWT in the treatment of DSWI is widely accepted and it will take more than results from a few retrospective studies to change this protocol. However, the results from our study combined with some recent publications raise serious questions about the safety and cost-efficiency of the current treatment protocols. Randomized studies or large multicentric trials would be highly beneficial in the future.

It would also be interesting to determinate if there are similar downsides of NPWT when it is used in other indications. Potentially, postponing reconstruction because of prolonged NPWT in other indications, for example in the treatment of pressure ulcers or diabetic foot ulcers, could carry similar disadvantages as described here.

It is likely that NPWT will continue to have a place in the treatment of DSWI in the future. It is very important to be able to recognize those patients that will benefit from the treatment. The aspect of patient selection should be a topic of future research.

The use of iNPWT with PICO™ to prevent DSWI seems ineffective. However, there are still many questions without definite answers. Earlier results indicate that there may be some patients with extremely high-risk profiles that would benefit this form of treatment after individual decision-making. The differences between PICO™ and Prevena™ in their capabilities to prevent wound complications have yet to be resolved. In addition, we were left to speculate whether iNPWT for two weeks would be more beneficial in elderly patients and patients with delayed wound healing. The development in medical technology is a rapidly evolving field and new iNPWT devices are being introduced. Nonetheless, it may be that the ideal device to be used in these indications has yet to be manufactured.

iNPWT after flap reconstruction seems to be beneficial. All of the published studies have investigated only small patient groups and thus further studies are warranted to verify the benefits of the treatment in a the statistically significant manner.

7 CONCLUSIONS

1. iNPWT with PICO™ seems ineffective in preventing DSWI in an institution with a relatively low infection rate.

2. The safety and cost effectiveness of NPWT in the treatment of DSWI are questioned. NPWT is associated with longer treatment periods, more visits to the operating room, and possibly even with higher mortality.

3. Preoperative NPWT and iNPWT with PICO™ after flap reconstruction may, however, be associated with fewer surgical complications after pectoralis major muscle flap reconstruction. In addition, iNPWT may lead to a shorter duration of hospitalization after flap reconstruction.

4. An IMAP fasciocutaneous flap with muscle sparing pectoralis major muscle flap is a useful option to cover complicated sternal defects. It may be used when the width of the defect excludes direct skin closure and instead of utilizing more distant flaps.

5. A split pectoralis major muscle flap is a versatile reconstruction method in the treatment of DSWI and suitable to be used as a first line reconstructive option.

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ORIGINAL PUBLICATIONS (I – IV)

I

Does incisional negative pressure wound therapy prevent sternal wound infections?

Myllykangas HM, Halonen J, Husso A, Väänänen H and Berg LT

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II

Negative pressure wound therapy in treatment of deep sternal wound infections – a critical appraisal

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III

Modified internal mammary artery perforator flap in treatment of sternal wound complications

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Modified Internal Mammary Artery Perforator Flap in Treatment of Sternal Wound Complications

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Objectivs There are multiple treatment strategies and flap options to cover defects after deep sternal wound infections and other similar sternal defects. The choice of flap is made according to surgeons' preferences and the size and location of the defect. Our aim is to introduce a new option to cover these kinds of defects with an internal mammary artery perforator flap combined with a pectoralis major muscle flap mostly raised with a muscle-sparing technique. **Design** We treated 13 patients with a sternal defect after cardiothoracic operations with this technique between 2010-2016. Ten patients had a deep sternal wound infection, two had an infection of the prosthesis after carotico-subclavian bypass and one had a fragmented sternum. Nine patients were treated with an internal mammary artery perforator fasciocutaneous flap with a muscle-sparing pectoralis major muscle flap and four patients with an internal mammary artery perforator fasciocutaneous flap combined with a right pectoralis major muscle flap. **Results** Three patients (23%) experienced major complications and four patients (31%) had conservatively treated minor complications. There were no flap losses. **Conclusion** This combination of flaps is a suitable option for patients with large defects in whom direct skin closure is not possible. It can be utilized for defects comprising the entire vertical length of the sternum. These are local flaps with a short operation time and are therefore most suitable for patients with comorbidities in whom major surgery is not an option.

Keywords: Cardiac surgical procedures / adverse effects, Medistinitis, Pectoralis muscle / transplantation, Perforator flap, Reconstructive surgical procedures / methods, Sternotomy / adverse effects, Sternum / surgery, Surgical flaps, Surgical wound infection / surgery

Introduction

Deep sternal wound infection (DSWI) is a rare but devastating postoperative complication of open-heart surgery. Recent reported incidence range from 0.96 to 2.5% [1-4]. The incidence rates in Finland have been reported to be 1.0-1.1% [5,6]. The post-sternotomy mediastinitis is associated with morbidity, multiple operations, prolonged hospital stay and high costs [7-9]. Mortality rates have been reported to lie in a range between 0 and 12.3% [2,4-6]. The declining numbers of sternotomies performed in recent years have resulted in the sub-selection of a group of patients with numerous comorbidities requiring operative treatment [2,6].

During the last decades, the treatment of sternal wound infections has evolved considerably leading to major improvements in both survival and morbidity [10]. There is, however, no consensus relating to the most suitable treatment strategy, timing and reconstructive technique [3,10,11]. Multiple treatment algorithms have been proposed in an attempt to standardize the management of this morbid complication, but none has achieved widespread general acceptance [4,5,10,12,13]. The treatment comprises a well-performed debridement of all devitalized tissue and removal of sternal wires, wound conditioning with negative pressure wound therapy, possible restabilization of the sternum and finally a reconstruction with tissue flaps. In our hospital, the treatment is handled as an interdisciplinary teamwork between cardiothoracic and plastic surgeons.

Various muscle flaps have been used. The use of flaps has been demonstrated to reduce mortality, morbidity, and chronic infections [10,14]. Studies have not been able to demonstrate significant differences between flap types [8]. The choice is more often made by taking into account the individual characteristics of the patient and experience of the surgeon. The flaps used in sternal reconstruction include pectoralis major muscle flap, rectus abdominis muscle or musculocutaneous flap, omentum, latissimus dorsi muscle or musculocutaneous flap, as well as their combination [15], and more recently a deep superior epigastric perforator (DSEP) flap [16]. Many of these options do not cover the entire length of the sternal defect or are associated with donor site morbidity and multiple potential complications including functional disability, hernias, seromas and pain [1,3,8,10,17-20].

The internal mammary artery perforator (IMAP) flap is a reliable and well described flap previously used for tracheostoma and head and neck reconstruction as well as covering small to medium -sized chest wall defects after tumor resection [21-24]. Its use for sternal defects after cardiothoracic wound complications, however, has been published only as case reports and a few small patient series [25]. Kannan et al. [26] used the IMAP flap in both a fasciocutaneous and a musculocutaneous form to cover sternal defects after sternotomy with dehiscence in seven patients without infections. Koulazouzidis et al. [27] used the IMAP fasciocutaneous flap in nine patients to conduct a sternal reconstruction after DSWI.

In this study, we describe our experience with the IMAP flap combined with mostly muscle sparing pectoralis major flap, for sternal wound coverage. Pectoralis major muscle flap is used as a split turnover flap based on IMA perforators. This technique was introduced to fill the need of a multimorbid patients that are not suited for major surgery with distant flaps but have a defect that cannot be covered by any form of pectoralis major muscle flap, for example because of a major skin defect.

Our study population comprises of ten patients with DSWI, one patient with an unstable and fragmented sternum and two patients with a deep wound infection and an exposed prosthesis after carotico-subclavian bypass. These three patients without a diagnosis of DSWI were included because they were subjected to a similar treatment protocol and reconstructive technique.

To our knowledge, this is the first study to describe this particular combination of flaps.

Materials and methods

Patients operated with the IMAP flap were identified from the operating room records. The data of these patients were collected by reviewing the medical records of the patients. The study was approved by the ethics committee of the Kuopio University Hospital.

Between the years 2010-2016, there were 13 IMAP flaps combined with pectoralis major muscle flap after cardiothoracic wound complications. All the operations were performed by the same senior plastic surgeon (L. T. B.). There were eight male and five female patients with an age range from 52 to 85 years (median 74 years). Nine patients had undergone coronary artery bypass grafting (CABG) and two patients had a cardiac valve replacement with CABG, one patient had thoracic endoprosthesis placement following carotico-carotico-subclavian bypass and one patient had carotico-subclavian bypass. The comorbidities and risk factors are shown in table 1. The patients' mean BMI was 33 kg/m^2. Four of the primary operations were emergency operations and five were urgent meaning that there were only four elective operations in this study population.

Table 1 – Comorbidities and risk factors

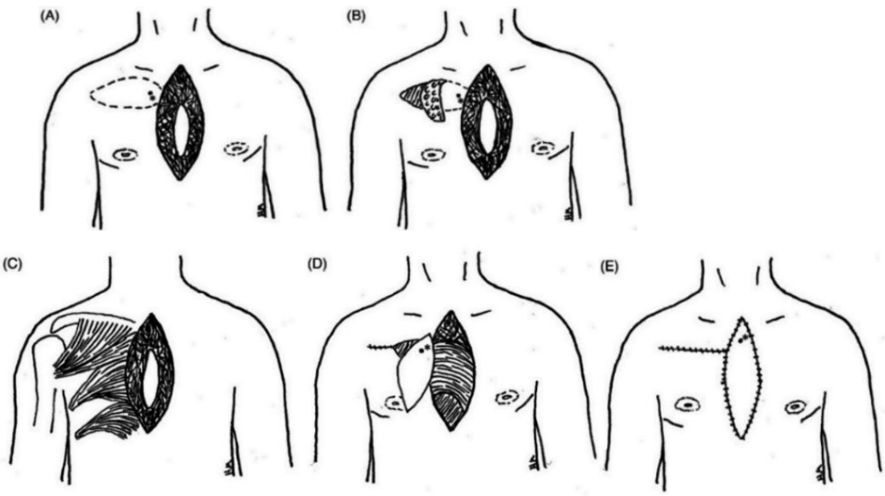
Comorbidities	Frequency	%
Obesity (BMI>30kg/m^2)	10	77
Smoking	2	15
Diabetes mellitus	5	38
Pulmonary disease	5	38
Renal failure	1	8
Hypertension	12	92
AMI	5	38
Multiple operations	1	8
Cancer	2	15
Non-elective operation	9	69

AMI= Acute myocardial infarction

Operative technique

The location of the IMA perforators was confirmed preoperatively with Doppler ultrasound. At first, the horizontally oriented skin flap was raised. After the assessment of the amount of muscle tissue needed, the pectoralis major muscle was raised from the thoracic wall using diathermia. A suitable section of the muscle was detached from the humerus and mobilized to the level of IMA perforators. The muscle was then split, if needed, by the muscle perforators. Depending on the size of the sternal defect, the muscle portion of the flap was divided into two or three portions. The muscle flaps as well as the fasciocutaneous flap were all based on the IMA perforators. In most of the operations, part of the muscle was left intact. The muscle was used to fill the cavity and then the skin flap was rotated 90 degrees to match the skin defect. These procedures are illustrated in figure 1. In most of the cases, incisional negative pressure therapy was used as a postoperative wound dressing after the wound had been appropriately closed. The antibiotic treatment was continued according to our normal protocol after the operation.

Figure 1. Schematic drawing of the procedure (A) Preoperative planning. Note the asterix marking the perforator. (B) Raising the fasciocutaneous flap (C) Schematic drawing of the muscle division (D) Muscle flaps installed to the sternal defect, fasciocutaneous flap still hanging free (E) Fasciocutanous flap installed on top of the muscle flaps.



Results

The median time from the primary operation until the diagnosis of DSWI was 17 days, ranging from three to 30 days. All but one of the operations were conducted in two-stages. The median period of time from diagnosis to the final reconstruction was 15 days, ranging from three to 177 days. The patient with the longest delay at first refused to undergo the operation and therefore there had been a very long attempt of closing the wound with negative pressure wound therapy that ultimately failed. In ten patients there was only one debridement, whereas two patients underwent from two to four debridements. Negative pressure therapy was used between the debridement and the final reconstruction in ten patients. The median period of time with negative pressure therapy was six days.

In nine patients, the reconstruction was conducted with an IMAP fasciocutaneus flap with a muscle sparing pectoralis major flap comprising one third to two thirds of the muscle, sometimes divided into two parts. In three patients, the entire right side of pectoralis major muscle was needed, due to a sternal defect, either as a divided turn over flap or as an advancement flap. No other flaps including the left pectoralis major muscle flap were needed in any of the patients. The median duration of the operation was 90 minutes including possible revision and refixation. Out of the ten patients with DSWI, refixation was possible in three patients and partly possible in two patients leaving four patients with a bony defect and one patient requiring sternum removal.

The median time in intensive care after reconstruction was one day, ranging from 0-14 days. The median length of hospitalization in the university hospital after the reconstruction was 12 days after which the patients were discharged to local hospitals (nine patients) or to their homes (two patients).

Two of the patients (15%) died during their hospitalization. The causes of death were not directly related to the flap reconstruction nor the DSWI. The first patient died of aortic rupture related to the primary operation ten days after the reconstruction and revealed no signs of any flap complications. The second patient died of kidney failure; hemodialysis was not initiated because of the multimorbidity of the patient. This patient had very severe DSWI with one resuscitation and multiple operations before it was possible to attempt reconstruction 102 days after the diagnosis of DSWI. Prior to the development of kidney failure and the subsequent death, the patient had displayed signs of local hematoma under the flap, a bedside revision was conducted, and local wound care initiated.

Complications were divided into major and minor depending on whether or not they demanded surgical treatment. Major complications were found in three (23%) of the patients including a hematoma in the donor-site and a partial necrosis of the tip of the flap, which was treated with a small skin graft. The most severe complication was a persistent infection leading to multiple operations and finally full recovery within one year. The IMAP flap itself stayed vital throughout the process of multiple debridements. Minor complications were found in four patients (31%) including one case of delayed wound healing at donor site with small opening measuring around 1.5 cm, two cases of small necrosis at the edge of the flap measuring 1 – 4 cm and one hematoma. Patient data and outcomes are shown in table 2.

Table 2 – Patient data and outcomes in our patient cohort

							Complications		
	Age	Gender	Operation	DSWI	BMI	i-NPWT	Minor	Major	Death
1	75	F	CABG	X	39	-	-	-	-
2	77	M	CABG	-	29	-	-	-	-
3	66	M	CABG	X	35	-	X	-	X
4	62	M	Carotic.	X	29	-	-	-	X
5	79	F	CABG	X	31	PICO	X	-	-
6	85	M	CABG + v	X	24	PICO	-	X	-
7	79	M	CABG	X	45	PICO	X	-	-
8	79	F	CABG	X	28	PICO	-	X	-
9	52	M	CABG	X	37	PICO	-	-	-
10	73	F	CABG	X	34	PICO	-	-	-
11	74	F	CABG + v	X	36	Prevena	X	-	-
12	56	M	CABG	X	33	Prevena	-	X	-
13	63	M	Carotic.	-	32	-	-	-	-

DSWI = Deep sternal wound infection
i-NPWT = Incisional negative pressure wound therapy
CABG = Coronary artery bypass grafting
CABG + V = CABG plus valve replacement
Carotic. = Carotico-subclavian bypass

Discussion

The most common muscle flap used in sternal reconstruction is the pectoralis major. It can be mobilized either as an advancement flap based on the thoracoacromial artery or as a turnover flap based on the internal mammary arterial blood supply. Bilateral flaps can be needed to obliterate sufficiently the dead space [1]. However, unilateral pectoralis major muscle flap and it's multiple modifications, including split muscle flap, are useful with many patients [28,29,30]. The operation is brief, and the muscles are easy to dissect. However, dividing the muscle's humeral insertion may lead to a functional defect [17,20,31]. The advancement flaps may not reach sufficiently to cover the defects in the most caudal third of the sternum. A direct closure of the skin is often attempted, although sometimes this can lead to unwanted tension and wound-healing problems [10,11,13]. With large defects, skin grafts have to be used leading to suboptimal cosmetic results [3,8].

The rectus abdominis muscle flap may be used if the pectoralis major muscle flap is unavailable or when it has an insufficient reach to the most caudal third of the sternum. This flap has a good volume and, if needed, it may also be used as a musculocutaneous flap. However, the flap, based on arteria epigastrica superior, may be unreliable if the ipsilateral IMA has been used in the primary operation. Possible complications include dehiscence of the abdominal wound, herniation and worsening of the lung function [8,32]. The omentum is another possible flap with a rich blood and lymphatic supply. The need of laparotomy introduces the risk of spreading the infection and the subsequent risk of hernia formation [8,18,33]. The latissimus dorsi muscle or musculocutaneous flap is a more rare reconstructive option. The flap can be used as a pedicled flap or as a free flap. However, raising a latissimus dorsi flap leads to a large donor site with possible hematoma and seroma formation [8].

In our hospital, the IMAP flap has not replaced the more simple pectoralis major muscle flap in cases where direct closure of the skin is feasible. First line treatment option for simpler defects in our treatment protocol is often unilateral turnover split pectoralis major muscle flap [5]. However, the IMAP flap is an option when there are wider defects comprising whole length of sternum where skin grafts or more distant flaps, such as rectus abdominis, omentum or even latissimus dorsi, would otherwise need to be considered. The IMAP flap is often chosen when the patient is not suitable for a more extensive operation or for undergoing laparotomy because of his/her comorbidities.

Using this flap in the most difficult cases explains the high complication rate (54% in total). However, usually this patient group consists of multimorbid patients, and the complication rates have also tended to be high in the other studies, being reported to range between 25.3-55.6% [4,10,19,27]. The two deaths in this small patient population increased the in-hospital mortality rate. This does not reflect the average mortality rate with DSWI in our hospital, which was 0% in a previous publication [5]. Furthermore, the deaths of these two patients were not related to the reconstructions.

In the previous study investigating IMAP flap in nine patients, the IMAP flap was used on its own [27]. In our study, the IMAP flap was most often combined with the muscle sparing pectoralis major muscle flap. This combination provided some extra tissue to cover wider and deeper defects without compromising the function of the upper arm with a considerable part of the muscle being left intact. The majority of the study group had a bony defect in their sternal area or only partial refixation of the sternum emphasizing the need for muscle tissue in addition to the fasciocutaneous flap.

Eight out of 13 patients in this study were treated with the incisional negative pressure therapy installed on the flap (PICO™ , Smith & Nephew, London, UK, in six patients; Prevena ™ Incision Management System, KCI, an Acelity Company, San Antonio, TX, in two patients). The study population is too small to draw any conclusions about the effectiveness of this treatment. However, in the previous study where the IMAP flap was used for sternal defects, there were two out of nine cases with dehiscence of the donor-site [26]. In our study, we did not encounter these complications, possibly partly because of the incisional negative pressure therapy used on the wounds.

There were five female patients in our study population. It has been speculated that the weight of the breast pulling the wound may result in dehiscence at the donor site [24,25]. We did not encounter any patient with dehiscence. It has been also speculated that IMAP flap is not suitable for women because of the visible scar at the donor site [25]. Our study population was elderly and multimorbid with large defects leaving few options for reconstruction. In these patients, the priority was to achieve wound closure with as little functional defect and as few major complication risks as possible. Possible scars at the donor site played a secondary role. The age of the female patients ranged from 73 to 79. There was some post-operative asymmetry of the breasts; this was treated with brassiere selection. Patients were informed of this almost inevitable consequence of the IMAP flap pre-operatively.

Figure 2. Preoperative and postoperative pictures of three patients. Pictures A and B represent a female patient with a very long attempt of negative pressure wound therapy after deep sternal wound infection that ultimately failed. Note the poor quality of the skin around the defect. Pictures C and D represent a male patient with a wide sternal defect where direct skin closure is not an option. Note the free style modification of the flap design in pictures E and F of a patient with absent second perforator.

The benefits of this flap combination include the reduction in donor-site morbidity, preservation of muscle function and the brief operation time with few of the late major complication risks more often associated with other reconstructive options. The dissection of the flap is relatively easy and straightforward. Independent arrangement of the muscle and skin flaps allows tailored reconstruction even with the most difficult defects. A few different modifications of the fasciocutaneus flap design options are illustrated in figure 2. The muscle portion of the reconstruction is individualized as well.

The main disadvantages include a visible scar at the donor-site and possible breast asymmetry. The bilateral use of internal mammary arteries in a primary cardiac operation can be a contraindication. Nonetheless, Kannan et al. [26] reported one case of the use of an IMAP flap even when both IMAs had been harvested four months earlier.

This study is limited by its retrospective nature and small study population. The data is collected only from the charts of the university hospital and may have omitted some minor late complications treated in the local hospitals. However, sternal reconstructions are not performed in any of these other hospitals and any relevant complications would have been referred back to our hospital for treatment. Additionally, most of the patients were subjected to a control assessment at the out-patient clinic a few months after surgery.

Conclusion

The IMAP fasciocutaneous flap with a muscle sparing pectoralis major muscle flap is a useful option for covering wide defects in the sternum after DSWI or similar sternal defects. It is most useful when the pectoralis major muscle flap with direct skin closure is not an option and when the patient is not suitable to be subjected to larger and possible more morbid reconstructions.

Declaration of interest. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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IV

Decreasing complications of pectoralis major muscle flap reconstruction with two modalities of negative pressure wound therapy

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Abstract

Background and objective: Deep sternal wound infection is a feared complication of open-heart surgery. Negative pressure wound therapy has gained an important role in the treatment of deep sternal wound infection. Incisional negative pressure wound therapy has been introduced as a method to prevent wound complications after sternotomy, and lately, after flap reconstructions in the treatment of deep sternal wound infection. We aimed to study if incisional negative pressure wound therapy with PICO™ had similar beneficial effect described earlier with competing commercial devices.

Methods: This study included 82 patients treated with pectoralis major muscle flap for deep sternal wound infection during the years 2006–2020. PICO group consisted of 24 patients treated with preoperative negative pressure wound therapy and postoperative incisional negative pressure wound therapy (PICO™). Two control groups included 48 patients with conventional treatment and 10 patients with preoperative negative pressure wound therapy only.

Results: In the PICO group, the complication rate declined from 50.0% to 33.30%, major complication rate from 29.2% to 12.5%, and need for an additional flap from 14.6.% to 4.2% when compared to conventional treatment. The length of hospital stay decreased as well. Preoperative negative pressure wound therapy alone was associated with moderate decline in the complication rates. In addition, we described the use of split pectoralis major muscle flap reconstruction in 57 patients. To our knowledge, this is the largest published patient series describing this method in the treatment of deep sternal wound infection.

Conclusions: Incisional negative pressure wound therapy with PICO™ seems beneficial after flap reconstruction. Split pectoralis major muscle flap is a versatile reconstruction option suitable to be used as a workhorse in the treatment of deep sternal wound infection.

Keywords

Mediastinitis, sternotomy, muscle flap, negative pressure wound therapy, surgical wound infection

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Introduction

Deep sternal wound infection (DSWI) is a rare but devastating complication of open-heart surgery. The incidence has varied between different publications but has been estimated at approximately 1% in the recent reports.[1–3] DSWI has been associated with increased mortality, prolonged hospitalization, morbidity, numerous re-operations, complications, and high costs.[2,4]

The treatment comprises of a well-performed debridement of devitalized tissue, removal of sternal wires, and administration of culture-specific antibiotics. The closure of the wound can be achieved in several ways using negative pressure wound therapy (NPWT), re-fixation of the sternum, and reconstruction with a variety of flap options.[5] A number of flap options, including muscle, musculocutaneous, and fasciocutaneous flaps as well as omentum, have been proposed.[5,6] However, in many centers, pectoralis major muscle flap has remained as a workhorse, because of the proximity to the wound, a constant vascular supply, and straight-forward operation technique without any additional skin incisions.[7,8] All of the flap options, including the pectoralis major muscle flap, have been associated with a relatively large number of complications augmented by the multimorbidity of this patient group.[7–10] There has been a wide variation in reporting of the complications; nonetheless, the total complication rate in various flap reconstructions has been described around 40%.[3]

Split pectoralis major muscle flap has been previously described but has remained less common reconstructive option when compared to the standard turnover or advancement techniques.[9,11,12] The split technique has been used to attain better reach for the most caudal part of the sternum. The complication rates of the split pectoralis major muscle flap have not been directly compared to other types of flaps.

NPWT has rapidly gained popularity in the treatment of DSWI either as a single treatment modality or as a bridge to reconstruction. Its disputed benefits include declined mortality rate and shorter hospital stay,[13,14] for example, although some recent studies have reported the opposite findings when comparing NPWT to early reconstruction.[15,16] In addition, incisional negative pressure wound therapy (iNPWT) has been used to prevent infections after open-heart surgery with mostly promising results.[17–20] Recently, there have been a few reports of using iNPWT after pectoralis major muscle flap reconstruction in the treatment of DSWI to prevent flap-related surgical complications.[10,21,22] Most of the studies concerning the use of NPWT and iNPWT have been relatively small retrospective studies with heterogeneity, possibility for publication bias, and the matter of manufacturer involvement to discuss.[23,24]

There are two leading commercially available NPWT systems for incisional wounds. Prevena™ (KCI, San Antonio, TX, USA) is a foam-based system with a canister and a continues pressure of −125 mm Hg. PICO™ (Smith & Nephew Ltd, Hull, UK) is a canister-free device with the pressure of −80 mm Hg. Prior studies have reported promising preliminary results using iNPWT after sternal flap reconstruction. In a study with 30 patients in the intervention group treated with Prevena™, the complication rate declined from 37.5% to 13.0%, and the major complication rate from 15.0% to 3.0%.[22] In a study with 19 patients treated with Prevena™, the rate of major complications declined from 32.1% to 5.3%.[10] A small study with 10 patients using Vivano System™ presented a decrease in the hospitalization length.[21] The superiority of one iNPWT system over another has not been defined. There is a meta-analysis that aimed to compare the two most used systems and favored Prevena™, but the study had significant clinical heterogeneity and was sponsored by the manufacturer of the Prevena™.[25]

In this study, we had two separate goals. Our first aim was to investigate if using PICO™ after pectoralis major muscle flap reconstruction would lead to similar decline in the complication rates that has earlier been described with competing iNPWT devices. Our second aim was to report our experience with split pectoralis muscle flap reconstruction as a workhorse in the sternal reconstructions after DSWI.

Materials and methods

Patients treated with pectoralis major muscle flap reconstruction were identified from the operating room records and information was manually collected from the patient records. Retrospective analysis was conducted. Institutional review board approval was not required for this non-interventional study according to national laws.

Between the years 2012 and 2020, there were 87 patients treated for DSWI with pectoralis major muscle flap in a single university hospital. To form comparable study groups, we excluded two patients because instant skin grafts were used in combination with the muscle flap. In addition, three patients with pectoralis major muscle flap and iNPWT with Prevena™ were excluded. Subsequently, all remaining 82 patients with the pectoralis major muscle flap were included and divided into three groups as follows: PICO group consisted of 24 patients treated with preoperative NPWT, pectoralis major muscle flap reconstruction, and postoperative iNPWT between the years 2012 and 2020; control group 1 consisted of 48 patients treated between 2006 and 2012 with pectoralis major muscle flap without any forms of NPWT; and control group 2 consisted of 10 patients treated between 2012 and 2017 with preoperative NPWT and pectoralis major muscle flap (Fig. 1).

Preoperative NPWT was not standardized, and multiple different commercial devices designed for open wounds were utilized. The length of preoperative NPWT varied from 3 to 174 days. Dressings were changed predominantly twice a week.

In the PICO group, single-use battery-powered iNPWT system (PICO™) was placed over closed wound in the operating room under sterile conditions. iNPWT was recommended to continue 7 days with a possible dressing change after 3 days. Multiple different sizes of PICO™ dressings were used, including 10 cm × 30 cm, 10 cm × 40 cm, and 25 cm × 25 cm, according to individual requirements.

The reconstructions with the split pectoralis major muscle flap or other modifications of the pectoralis major muscle flap were carried out by several senior cardiothoracic and plastic surgeons. The split pectoralis major muscle flap was

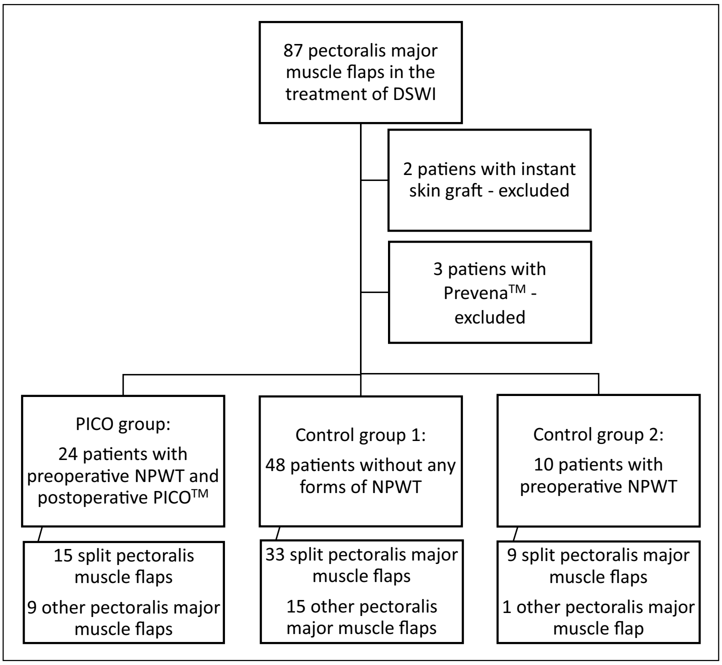

Fig. 1. The study design.

raised by splitting of the muscle into two or three parts based on the internal mammary artery perforators and handled as independent turnover flaps (Fig. 2). The technique has been described in more detail by Li et al.[11] in 2004.

The outcomes were measured by the complications requiring treatment in the university hospital. Complications requiring operative treatment were defined as major. Complications requiring active local wound care, antibiotics, prolonged hospitalization, and/or additional visits to the hospital were defined as minor. Follow-up time ranged from 14 years to 3 months.

We included only patients with prior DSWI, which was diagnosed based on the guidelines by the Centers for Disease Control and Prevention in the United States. The diagnosis of DSWI required at least one of the following:

1. An organism isolated from culture of mediastinal tissue or fluids.
2. Evidence of mediastinitis seen during the operation.
3. One of the following conditions: chest pain, sternal instability, or fever (>38 °C), in combination with either purulent discharge from the mediastinum or an organism isolated from the blood culture.

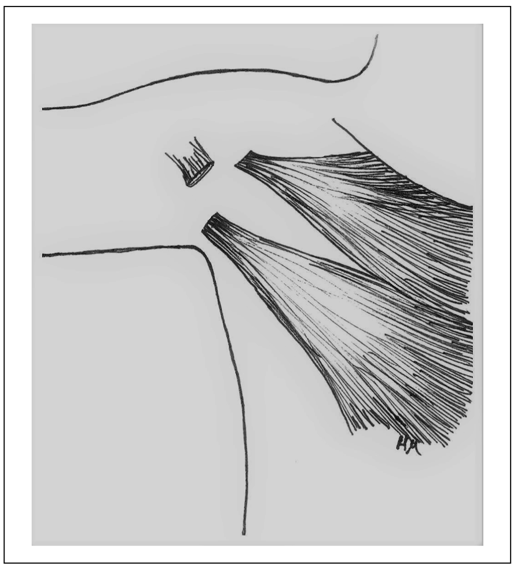

Fig. 2. Schematic drawing of splitting of the muscle.

The statistical analyses were performed using IBM SPSS statistics 27.0 software for Windows (SPSS Inc., Chicago, IL, USA). Intention to treat analysis was conducted. Categorial variables were reported as frequencies and percentages. Continuous variables were reported as mean values and standard deviations. The Mann–Whitney *U* test was used as a non-parametric test to compare two unpaired groups. To

Table 1. Pectoralis major muscle flap, various forms.

	n = 87	All complications	Major complications	Need for an additional flap
Split pectoralis	57	21 (36.8%)	9 (15.8%)	5 (8.9%)
Monolateral turnover	6	2 (33.3%)	2 (33.3%)	1 (16.7%)
Bilateral turnover	2	1 (50.0%)	1 (50.0%)	–
Monolateral advancement	3	3 (100.0%)	2 (66.7%)	1 (33.3%)
Bilateral advancement	6	5 (66.7%)	4 (66.7%)	3 (50.0%)
Turnover + advancement	1	1 (100.0%)	–	–
With IMAP flap	10	7 (70.0%)	3 (30.0%)	1 (10.0%)
With skin graft	2	2 (100.0%)	–	–

IMAP: internal mammary artery perforator.

compare categorial variables, Fisher's exact test was used when there were <5 expected values in any of the cells of a contingency table. In other cases, the Pearson chi-square test was used.

Results

There were 87 patients treated with the pectoralis major muscle flap for DSWI in the Kuopio University Hospital between the years 2006 and 2020. Most of the patients (65.5%) were treated with the split pectoralis major muscle flap. This was the most common reconstructive option in all of the study groups, constituting 62.5% of the flaps in the PICO group, 68.8% of the flaps in the control group 1, and 90.0% of the flaps in the control group 2. However, other modifications—including monolateral and bilateral advancement flaps, monolateral and bilateral turnover flaps without splitting, split pectoralis major muscle flap with internal mammary artery perforator flap, turnover flap with skin graft, and turnover flap combined with contralateral advancement flap—were used when needed. Different techniques and their complications are listed in Table 1 to demonstrate the wide range of reconstructive options. In our material, the split pectoralis major muscle flap was associated with less complications compared to other forms of the pectoralis muscle flap reconstruction.

The basic characteristics of the three patient groups are represented in Table 2. The distribution of age, obesity, and other co-morbidities, including diabetes, seemed relatively even between the groups. There were only slightly higher EuroSCORE II values in the PICO group. Smoking was more common in the control group 2.

The complication rates were compared between the PICO group and the control group 1. The rate of all complications was 33.0% in the PICO group and 50.0% in the control group 1, with non-statistical difference ($P = 0.180$). The rates of major complications were 29.2% and 12.5%, respectively ($P = 0.148$). Only one additional flap was needed in the PICO group whereas seven additional flaps were needed in the control group 1 ($P = 0.255$). The complications are further described in Table 3. The greatest decline was seen with bleeding complications and partial flap necrosis, although the groups were too small to draw any definitive conclusions. The complication rates in the control group 2 laid in between the complication rates in the two other groups.

Before the adaptation of NPWT and iNPWT into the treatment protocol, the flap-related complication rates showed no tendency to decline over time. The complication rate was 45.8% with the first 24 patients in the control group, operated between 2006 and 2009, and 54.2% with the second 24 patients, operated between 2009 and 2012.

The length of hospital stay after flap reconstruction as well as the length of stay at the intensive care unit after flap reconstruction were shorter in the PICO group when compared to the control group 1 ($P = 0.914$ and $P = 0.096$, respectively). The length of the hospital stay was even longer in the control group 2, but the small number of patients in this group must be considered when interpretating the results.

Discussion

Our results using PICO™, with the decrease in major complications from 29.2% to 12.5%, were in line with the previous studies.[10,21,22] However, it seemed that some of the decline in

Table 2. Pre- and intraoperative data.

	PICO group (*n* = 24)	Control group 1 (*n* = 48)	Control group 2 (*n* = 10)
Age, mean ± SD	71.1 ± 9.5	67.0 ± 9.3	69.4 ± 7.0
Female	15 (62.5%)	29 (60.4%)	8 (80%)
CABG	14 (58.3%)	42 (87.5%)	7 (70.0%)
CABG + v	4 (16.7%)	4 (8.3%)	2 (20.0%)
Aorta	3 (12.5%)	1 (2.1%)	1 (10.0%)
Diabetes	12 (50.0%)	25 (52.1%)	5 (50.0%)
Kidney disease	3 (12.5%)	4 (8.3%)	2 (20.0%)
Heart failure	3 (12.5%)	10 (20.8%)	2 (20.0%)
ASO	3 (12.5%)	5 (10.4%)	1 (10.0%)
Lung disease	7 (29.2%)	9 (18.8%)	2 (20.0%)
MCI	14 (58.3%)	20 (41.7%)	5 (50.0%)
Smoking	3 (12.5%)	6 (12.5%)	5 (50.0%)
BMI, mean ± SD	29.8 ± 5.4	30.2 ± 5.8	30.6 ± 4.3
EuroSCORE II, mean ± SD	4.2 ± 3.4	3.9 ± 3.9	3.8 ± 2.2

ASO: peripheral arterial disease; BMI: body mass index; CABG: coronary artery bypass grafting; CABG + v: coronary artery bypass grafting and valve replacement; MCI: prior myocardial infarction; SD: standard deviation.

the complication rates could be due to the preconditioning of the wound with NPWT. NPWT was adapted into clinical practice just before adapting iNPWT. This matter has not been discussed in the previous studies. The prevalence of NPWT was either not mentioned,[10,22] or higher in the iNPWT group, as was the case in this study design as well.[21]

In our hospital, PICO™ became a regularly used part of the treatment protocol after sternal flap reconstructions in 2012. The benefits of PICO™ include economical price and ease of use. However, with long or multiform skin incisions, Prevena™ has the benefit of allowing more individual tailoring and fitting of the wound dressing. Since all published results rely on small patient groups, the superiority of one system over another cannot be estimated. In the future, a randomized study concerning the subject would be highly interesting.

Interestingly, the length of hospital stay was shorter in the PICO group when compared to either of the control groups. Consequently, it seems that the shorter hospital stay was associated with postoperative iNPWT rather than preoperative wound conditioning. This may be due to faster wound healing and more confident early mobilization of the patients with iNPWT. Shorter hospitalization periods, if verified in future studies, would yield to certain cost-effectiveness of iNPWT.

In our hospital, the split pectoralis major muscle flap reconstruction is the most common reconstructive method used in the treatment of DSWI. The technique is preferred because of the ability to tailor the muscle portions according to the individual requirements (Fig. 3). The reach into the most caudal part of the sternum is superior in comparison with advancement or standard turnover flap design. The split pectoralis muscle flap remains less widely used when compared to other modifications of the pectoralis major muscle flap. The technique is, although fast and straight-forward in experienced hands, slightly more technically demanding when compared to other forms of the pectoralis major muscle flap. As far as we are aware, this is the largest patient series published reporting the use of this flap option in the treatment of DSWI.

We included, however, all forms of the pectoralis major muscle flap reconstruction in this study. Multiple different

Table 3. Complications.

	PICO group (*n* = 24)	Control group 1 (*n* = 48)	Control group 2 (*n* = 10)
All complications	8 (33.3%)	24 (50.0%)	4 (40.0%)
Major complications	3 (12.5%)	14 (29.2%)	2 (20.0%)
Bleeding	1 (4.2%)	8 (16.7%)	2 (20.0%)
Dehiscence	4 (16.7%)	7 (14.6%)	1 (10.0%)
Infection	1 (4.2%)	3 (6.3%)	2 (20.0%)
Partial necrosis	3 (12.5%)	13 (27.1%)	1 (10.0%)
Fistula	0 (0%)	3 (6.3%)	1 (10.0%)
Another flap	1 (4.2%)	7 (14.6%)	1 (10.0%)
Hospital stay, mean ± SD[a]	12.8 ± 8.6	22.1 ± 42.1	30.1 ± 40.9
ICU stay, mean ± SD[a]	4.6 ± 7.5	8.0 ± 19.67	10.6 ± 22.2

SD: standard deviation; ICU: intensive care unit.
One patient may have more than one complication.
[a]After reconstruction.

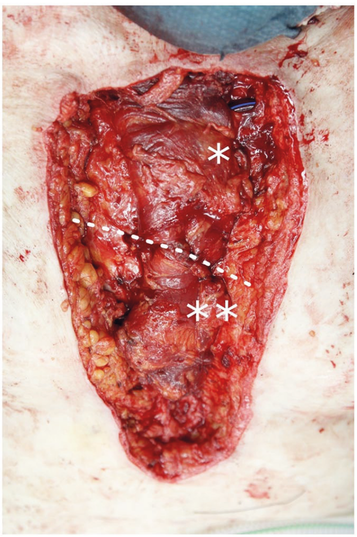

Fig. 3. Split pectoralis major muscle flap with *cranial part and **caudal part combined is sufficient to cover the whole length of sternum.

ways to use the pectoralis major muscle flap were used when needed. The complication rates with different forms of the flap were described, but potential selection bias prevented further analysis. It seemed, however, that complication rates with the split pectoralis major muscle flap were highly comparable. The size and location of the defect, the ability to reach direct skin closure, the existence of the intact internal mammary arteries, and the experience of the surgeon are some factors influencing the choice of flap.

The major limitation of this study is the retrospective study design and the limited number of patients in each group. However, considering the rarity of DSWI and the subsequent flap reconstructions, randomized study design remains challenging. All previous reports concerning the subject have been retrospective studies with relatively small study groups and historical control group, as was the case in this study as well. Thus, all results remain preliminary. Further studies with larger study groups or meta-analysis are warranted to draw any definite conclusions of the benefits of iNPWT after flap reconstruction.

Conclusion

NPWT seems to have beneficial effect on the rate of surgical complications related to flap reconstruction. Although preoperative preconditioning of the wound with NPWT seems to play its part, some additional benefit with iNPWT can be seen. iNPWT may also be useful to achieve shorter hospitalization periods. The split pectoralis major muscle flap is a versatile reconstruction option suited to be used as a workhorse in the treatment of DSWI.

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Deep sternal wound infection is a rare but devastating complication of open-heart surgery. Our results challenged the current treatment algorithm utilizing negative pressure wound therapy as the first-line treatment option. Accordingly, incisional negative pressure wound therapy was not considered beneficial in the prevention of sternal wound infections. In addition, we described two less commonly used flap reconstruction methods in the treatment of sternal wound infections.

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