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Kommissarischer Direktor: Prof. Dr. med. Ingo Eitel

Efficacy and Safety of Glycoprotein IIb/IIIa Receptor Antagonists in Patients with Infarct-Related Cardiogenic Shock

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Amr Abdin

aus Damaskus, Syrien

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1. Berichterstatter/Berichtrstatterin: **Prof. Dr. med. Ingo Eitel**
2. Berichterstatter/Berichterstatterin

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Outline

List of Abbreviations:

ACS	*Acute Coronary Syndrome*
AMI	*Acute Myocardial Infarction*
CABG	*Coronary Artery Bypass Graft*
CAD	*Coronary Artery Disease*
CVA	*Cerebrovascular Accident*
CO	*Cardiac Output*
CS	*Cardiogenic Shock*
ECG	*Electrocardiography*
ECLS	*Extracorporeal Life Support*
ECMO	*Extracorporeal Membrane Oxygenation*
GUSTO-1	*Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries*
HR	*Hazard Ratio*
IABP	*Intra-aortic Balloon Pump*
ICU	*Intensive Care Unit*
LV	*Left Ventricle*
LVAD	*Left Ventricular Assist Device*
LVEF	*Left Ventricular Ejection Fraction*
MAP	*Mean Arterial Pressure*
MCS	*Mechanical Circulatory Support*
MODS	*Multiorgan Dysfunction Syndrome*
PCI	*Percutaneous Coronary Intervention*
PCWP	*Pulmonary Capillary Wedge Pressure*
PiCCO	*Pulse Contour Cardiac Output*
PURSUIT	*The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy*

SHOCK	*Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock*
STEMI	*ST-elevation Myocardial Infarction*
TIMI	*Thrombolysis In Myocardial Infarction*

List of Figures

List of Tables

1. Introduction

Cardiogenic shock (CS) is a clinical condition of decreased tissue (end-organ) perfusion as a result of cardiac dysfunction [1]. CS continues to complicate approximately 5% to 8% of ST-elevation-myocardial infarction (STEMI) and 2.5% of non-STEMI cases with approximately 60,000 to 70,000 cases in Europe and 40,000 to 50,000 cases per year in the United States [1,2].

The most common cause of CS is ventricular failure following acute myocardial infarction (AMI). Mechanical complications can also lead to CS such as acute mitral regurgitation, ventricular septal and free wall rupture. Other possible causes for CS are decompensated valvular heart disease, acute myocarditis and arrhythmias [1,2].

The short-term prognosis of CS is very poor and directly related to the severity of the haemodynamic disorder and patients most commonly proceed to multiple organ dysfunction syndrome (MODS) due to ongoing organ hypoperfusion [2]. Decreased coronary perfusion pressure and increased myocardial oxygen demand play a major role in the vicious cycle that leads to an impaired cardiac output with subsequent severe tissue hypoperfusion and ultimately death [2]. The historic mortality rate of CS complicating AMI was 80 to 90% [3]. However, lower in-hospital mortality rates have been reported in recent studies, ranging from 48 to 74% [4,5]. Evidence of continued improvement in mortality from CS between 1994 and 2006 was shown from two reports from the national registry of myocardial Infarction [5] and a large Swiss registry [6]. However, despite treatment improvement including early revascularization, CS remains the most common cause of death in AMI with mortality rates still approaching 40 to 50% [4]. Consequently, CS is an emergency, which requires rapid diagnosis and initiation of pharmacologic and/or interventional therapy to maintain the blood pressure and CO. All patients with CS require prompt admission to the intensive care unit and a rapid evaluation to improve the outcome [3].

In infarct-related CS early restoration of coronary blood flow is the most important intervention for improving survival and has emerged as the standard therapy for patients with CS following

myocardial ischaemia [2]. The pivotal SHOCK (*Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock*) trial demonstrated that overall mortality can be significantly reduced by 38% when coronary reperfusion is established and this survival benefit with early revascularization has been also confirmed by other studies and registries [4]. However, the restoration of normal epicardial flow by percutaneous coronary intervention (PCI) in CS is lower in comparison to non-CS patients. Importantly, such failure to achieve normal flow in the infarct-related coronary artery impacts mortality [7]. In the setting of CS, the onset of action of oral antiplatelets (e.g. clopidogrel, ticagrelor, prasugrel) is impaired. Bioavailability of these oral antiplatelets may also be decreased due to delayed intestinal absorption, use of opiates, therapeutic hypothermia, or intubation. Therefore, intravenous glycoprotein (GP) IIb/IIIa receptor antagonists may be beneficial in CS [2]. In high-risk patients with STEMI, several trials and meta-analysis documented clinical benefits of GP IIb/IIIa receptor antagonists as adjunct to primary PCI [8]. The current guidelines support a liberal use of GP IIb/IIIa receptor antagonists in PCI cases with high thrombus burden and slow flow after PCI especially in patients with CS (Class IIa recommendation) [2]. However, the impact of GP IIb/IIIa receptor antagonist therapy on mortality in patients with AMI complicating CS undergoing stent implantation is unclear and further data are needed to investigate a potential benefit of GP IIb/IIIa receptor antagonists in infarct-related CS [2, 9, 10].

The aim of this work was therefore to assess the efficacy and safety of GP IIb/IIIa receptor antagonists in patients with CS as a predefined substudy from the largest CS trial to date the *Intraaortic Balloon Pump in Cardiogenic Shock II* (IABP-SHOCK II) trial. This randomized, multicentre trial randomized 600 patients with CS complicating AMI undergoing early revascularization therapy to an additional therapy with or without intra-aortic balloon pump support (IABP). The study showed that additional IABP use did not significantly reduce 30-day and 12-month mortality in patients with CS complicating AMI [11, 12]. In the current predefined substudy, we compared the effect of GP IIb/IIIa receptor antagonists in these patients with regard to baseline and procedural characteristics as well as short- and long-term clinical outcome.

2. Background

2.1 Cardiogenic Shock

2.1.1 Definition, Incidence and Population Trends

CS is a physiologic state that results from cardiac dysfunction. It is a medical emergency caused by a variety of acute and chronic disorders, commonly occurring after AMI. Despite the patient having a normal intravascular volume, the cardiac dysfunction leads to end organ hypoperfusion [1].

CS is defined by the following main diagnostic criteria [2,13]:

- Cardiac index <1.8 L/min/m^2 without support or <2.0 to 2.2 L/min/m^2 with support.
- Systolic blood pressure 90 mmHg for 30 min or vasopressors needed to reach a blood pressure ≥90 mmHg.
- Elevated filling pressure (Pulmonary capillary wedge pressure [PCWP] 15-18 mmHg) with:

  1) Evidence of tissue hypoperfusion presented as altered mental status.

  2) Oliguria with urine output 30 mL/h.

  3) Cold extremities and/or arterial lactate >2.0 mmol/L

However, CS diagnosis can usually be made by clinical assessment without advanced haemodynamic monitoring [2].

The precise incidence of CS is difficult to measure because patients who die before reaching the hospital are not adequately diagnosed as CS [14]. In previous studies the incidence rates of CS after AMI have ranged from 5% to 15%. This relatively wide range reflects the various definitions of AMI and CS used, selected patient cohorts, the time periods under study, and the use of therapeutic options that may reduce the risk of CS. However, overall the incidence of CS appears to be falling since the mid-1970s. In a report from a United States metropolitan area (Worcester, Massachusetts), the incidence of CS was around 7% between 1975 and 1990 and has decreased to 5.5 to 6.0% thereafter [1].

The overall incidence of CS is higher in men than in women, with females accounting for 42% of patients with CS. This difference results from the increased prevalence of coronary artery disease in males. However, a higher percentage of female patients with AMI develop CS as compared to males with MI [15].

Median age for CS reflects the bimodal allocation of the disease. The median age of adult patients ranges from 65 to 76 years. For younger adults or children, CS occurs mainly as a result of congenital heart disease or fulminant myocarditis [15].

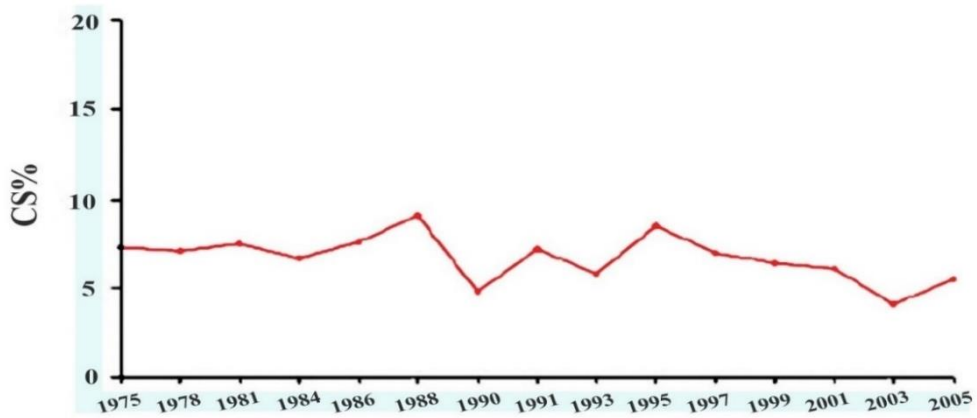

Figure1: Trends in the incidence rates of CS in patients with AMI. Adapted from [16].

2.1.2 Aetiology

Extensive AMI is the most common cause of CS. However, a small infarction in a patient with preexisting impaired LV function can also cause CS. It is necessary to know that large areas of nonfunctional but viable myocardium may contribute to the CS in patients after AMI. Mechanical complications can also cause CS — such as acute mitral regurgitation, rupture of the interventricular septum, or rupture of the free wall — or by large right ventricular infarctions. Other causes of CS include myocarditis, end-stage cardiomyopathy, myocardial contusion, septic shock with severe myocardial depression, myocardial dysfunction after prolonged cardiopulmonary bypass, valvular heart disease, and hypertrophic obstructive cardiomyopathy (Table 1) [17]. In a report of the SHOCK trial registry of 1160 patients with CS, 74.5% of patients had LV failure, 8.3% had acute mitral regurgitation, 4.6% had ventricular septal

rupture, 3.4% had isolated right ventricular shock, 1.7% had tamponade or cardiac rupture, and 8% had CS as a result of other causes [17,18]. In the SHOCK trial registry, 75% of patients developed CS within 24 hours after presentation and 7 hours was the median delay from onset of infarction.

Table 1: Causes of CS. Adapted from [19].
AMI: acute myocardial infarction. **LV:** left ventricule.

Causes of CS
AMI
Pump failure
Large infarction
Smaller infarction with pre-existing LV dysfunction
Reinfarction
Infarction extension
Mechanical complication
Acute mitral regurgitation caused by papillary muscle rupture
Ventricular septal defect
Free wall rupture
Pericardial tamponade
Right ventricular failure
Other conditions
End-stage cardiomyopathy
Myocarditis
Myocardial contusion
Septic shock with sever myocardial depression
LV outflow tract obstruction
Aortic stenosis
Hypertrophic obstructive cardiomyopathy
Obstruction to LV filling
Mitral stenosis
Left atrial myxoma
Acute mitral regurgitation (chordal rupture)
Acute aortic insufficiency

2.1.3 Pathophysiology

CS is characterized by systolic and diastolic dysfunction. CS patients as a result from AMI usually have evidence of progressive myocardial necrosis with subsequent large areas of infarcted myocardium. Diminished coronary perfusion pressure and increased myocardial oxygen demand assume a major role in the vicious cycle that causes CS. Patients experiencing CS frequently have restricted coronary blood flow reserve resulting from multivessel coronary artery disease. Myocardial diastolic function is usually also affected,

because ischaemia leads to decrease myocardial compliance, therefore increasing LV filling pressure, which may finally cause pulmonary oedema (Figure 2). Autopsy studies demonstrated that CS is commonly combined with more than 40% loss of the LV myocardial muscle [20].

2.1.3.1 Cellular Pathology

Cellular hypoxia as a result from tissue hypoperfusion causes anaerobic glycolysis, intracellular acidosis and accumulation of lactic acid. Moreover, reduction in transmembrane potential and intracellular accumulation of sodium and calcium as a result from myocyte membrane transport pump failure, lead to myocyte swelling [20, 21].

In the setting of severe and prolonged ischaemia, myonecrosis develops from irreversible myocardial cell damage, which incorporates swelling of the mitochondrial, lysosomal breakdown, and the accumulation of denatured proteins and chromatin. These occasions induce a break of the mitochondria, atomic envelopes, and plasma films. Also, apoptosis (programmed cell death) may emerge in peri-infarcted zones and may prompt myocyte loss. Inflammatory cascade activation and stretching of the myocytes generates factors that overwhelm inhibitors of apoptosis with final induction of apoptosis [21].

2.1.3.2 Reversible Myocardial Dysfunction

Dysfunctional large myocardium areas, which are still viable, play a role in development of CS in patients with AMI. Myocardial stunning or hibernating myocardium are primarily characterized by reversible dysfunction of the myocardium. Despite the fact that hibernation describes another physiologic concept than myocardial stunning, the conditions are hard to separate in the clinical setting and they regularly exist together [22].

Postischaemic dysfunction that persists in spite of restoration of normal blood flow is described as myocardial stunning. This dysfunction can persist for several hours after transient non-lethal ischaemia but is eventually followed by full functional recovery [21,23].

In the setting of severely reduced coronary blood flow, hibernating myocardium is defined as persistently myocardial dysfunction at rest. Hibernation appears to be an effective adaptive response to hypoperfusion which may reduce the risk for further ischaemia or necrosis. The improvement of myocardial function can be achieved by revascularization of the hibernating (and/or stunned) myocardium.

Because of their therapeutic implications, hibernating and stunning myocardium are very important phenomena in CS. Hibernating myocardium improves with revascularization, while an inotropic effect can stimulate the stunned myocardium which keeps an inotropic reserve [24].

2.1.3.3 Cardiovascular Mechanics of CS

Because of the reduction in contractility, a right shift of the LV end-systolic pressure-volume curve represents the main mechanical defect in CS. Therefore, the ventricle's ability to eject less blood volume per beat remains possible at even lower systolic pressure. As a result, the end-systolic volume increases [23], whereas the stroke volume is decreased, and to compensate for this, the diastolic pressure-volume curve also shifts to the right. This leads to increased diastolic filling, which is associated with an increase in end-diastolic pressure. Consequently, the effort to increase CO by this mechanism will increase myocardial oxygen needs and cause pulmonary oedema.

2.1.3.4 Systemic Effects

Stroke volume and CO are diminished when a large area of LV myocardium gets ischaemic and unable to pump effectively. Myocardial ischaemia is further exacerbated by compromised myocardial perfusion. Due to hypotension and tachycardia, myocardial ischaemia is provoked by depressed myocardial perfusion [23,25]. The pump failure increases with increased ventricular diastolic pressures, leading to additional wall stress and therefore elevating myocardial oxygen requirements.

Decreased CO reduces systemic perfusion. This usually leads to tissue hypoperfusion with anaerobic metabolism and lactic acid formation. These effects result in worsening of LV systolic function and impaired myocardial mechanics.

Moreover, depressed myocardial function prompts the initiation of many physiologic compensatory reactions. These include activation of the sympathetic system, which increases the heart rate and causes renal fluid retention, subsequently increasing the LV preload. This response leads to further worsening of myocardial ischaemia.

Fluid overload and LV diastolic filling impairment lead to pulmonary venous congestion and hypoxaemia. Vasoconstriction mediated by the sympathetic system in order to keep systemic blood pressure enhances myocardial afterload, which decreases cardiac function. Finally, myocardial ischaemia will increase as a result of excessive myocardial oxygen demand with simultaneous insufficient myocardial perfusion, starting a vicious cycle that finally ends in death (Figure 2).

As already mentioned, patients with CS usually have a combination of systolic and diastolic myocardial dysfunction. Impaired myocardial compliance resulting from myocardial ischaemia leads to LV filling pressure elevation at a given end-diastolic volume, which causes congestive heart failure [25].

2.1.3.5 Shock State

Shock state is defined as a syndrome of tissue hypoxia and vital organ dysfunction resulting from acute systemic hypoperfusion. All types of shock are characterized by reduced tissue perfusion, especially of the end organs including the brain, heart, and kidneys [20]. A decrease in higher cortical performance leads to brain perfusion reduction, which is characterized by an impaired mental status ranging from confusion to deep coma. Diminished coronary perfusion results in worsening of cardiac dysfunction that provokes a vicious cycle of global tissue hypoperfusion. As a result, the kidneys try to compensate by reducing glomerular filtration, causing oliguria and finally renal impairment.

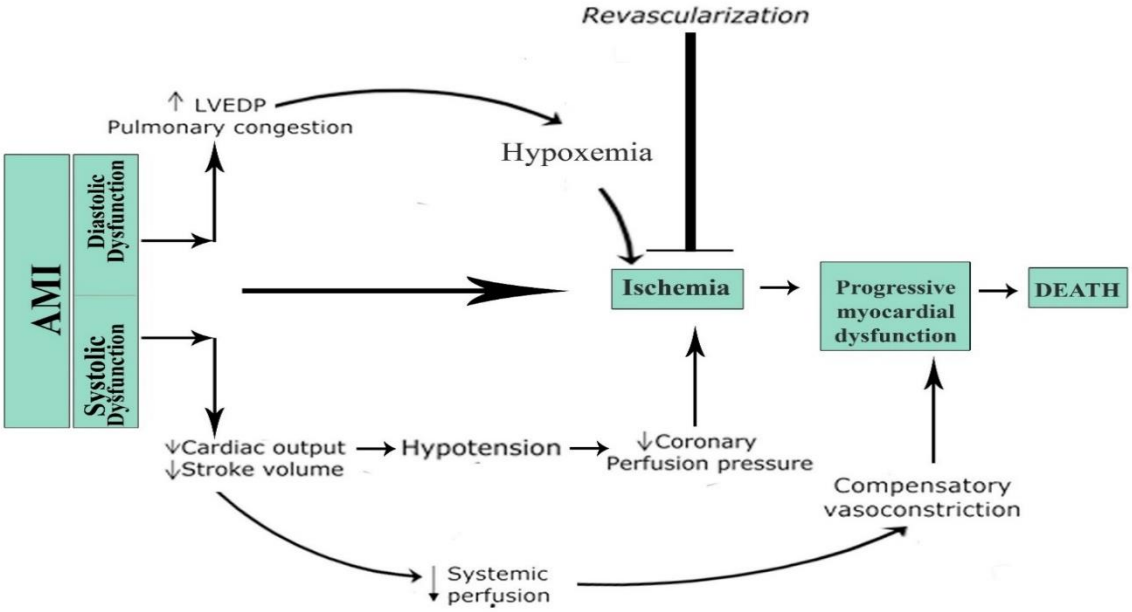

Figure 2: Current concept of CS pathophysiology.
Myocardial injury causes systolic and diastolic dysfunction. A decrease in CO leads to a decrease in systemic and coronary perfusion. This exacerbates ischaemia and causes cell death in the infarct border zone and the remote zone of myocardium. Inadequate systemic perfusion triggers reflex vasoconstriction, which is usually insufficient. Systemic inflammation may play a role in limiting the peripheral vascular compensatory response and may contribute to myocardial dysfunction. Adapted from [1].
AMI: acute myocardial infarction. **LVEDP:** left ventricular end-diastolic pressure.

2.1.4 Diagnostic Workup

As previously mentioned, the key to have improved outcomes in CS is a rapid diagnosis to promote supportive therapy and early coronary artery revascularization in infarct-related CS. The work-up in CS consists of many important investigations such as laboratory studies and electrocardiography (ECG). Moreover, the diagnostic work-up may include imaging studies like echocardiography and chest X-ray; and invasive haemodynamic monitoring [26].

2.1.4.1 Electrocardiography

ECG is an essential part in the diagnosis of AMI, particularly STEMI. The diagnosis of STEMI can be made in the presence of ST-segment elevation according to the following criteria: New ST elevation in two contiguous leads of >0.1 mV in all leads other than leads V2-V3, in which the cut point is ≥0.2 mV in men ≥40 years, ≥0.25 in men <40 years and ≥0.15 mV in women [27] (Figure 3).

Moreover, in case of non-STEMI or unstable angina ST depression, Q-waves or ventricular tachycardia as a result from myocardial ischaemia might be seen. A normal ECG, on the other hand, does not exclude the possibility of AMI [28].

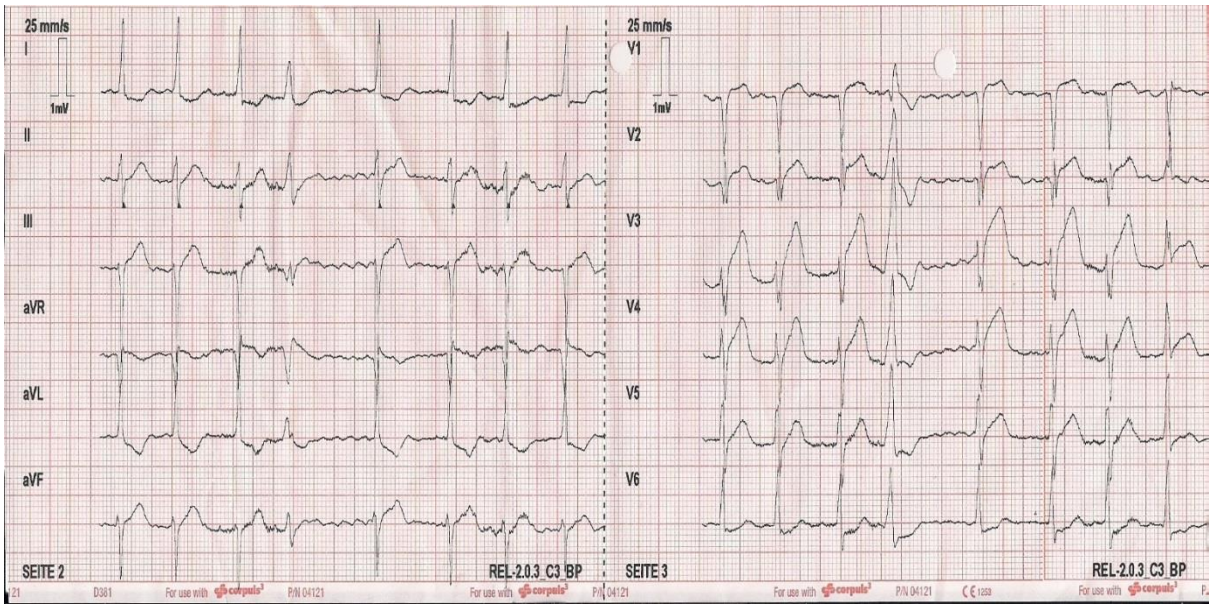

Figure 3: Patient with AMI developing subsequent CS.

2.1.4.2 Imaging Studies

2.1.4.2.1 Echocardiography

Echocardiography is an essential early diagnostic tool in CS providing important information about systolic and diastolic dysfunction. Moreover, a rapid diagnosis of the mechanical causes of CS can be established such as acute ventricular septal defect, pericardial tamponade and free myocardial wall rupture [29]. Furthermore, echocardiography can show areas of ventricular wall motion abnormalities or can reveal valvular dysfunction. However, LVEF is not always reduced in CS as shown in the SHOCK trial registry [4].

2.1.4.2.2 Chest Radiography

Chest radiographic findings may be valuable to rule out other causes of shock or chest pain. A widened mediastinum may indicate aortic dissection. Tension pneumothorax or pneumomediastinum recognized on radiographic films might present as low-output shock. The majority of patients with CS show findings of LV failure with pulmonary vascular redistribution, cardiomegaly, interstitial pulmonary oedema and bilateral pleural effusions [22].

2.1.4.3 Coronary Artery Angiogram

An early coronary angiogram is indicated in all patients presenting with infarct-related CS. Angiography is important to determine the anatomy of the coronary arteries and the requirement for urgent revascularization. Multi-vessel coronary artery disease is a common finding among 70-80% of CS patients [2]. Coronary angiogram provides not only information about the coronary artery disease but also measurements of oxygen saturation and CO by performing left ventriculography. Moreover, left ventriculography can be used to assess the appearance and wall motion abnormalities of the LV.

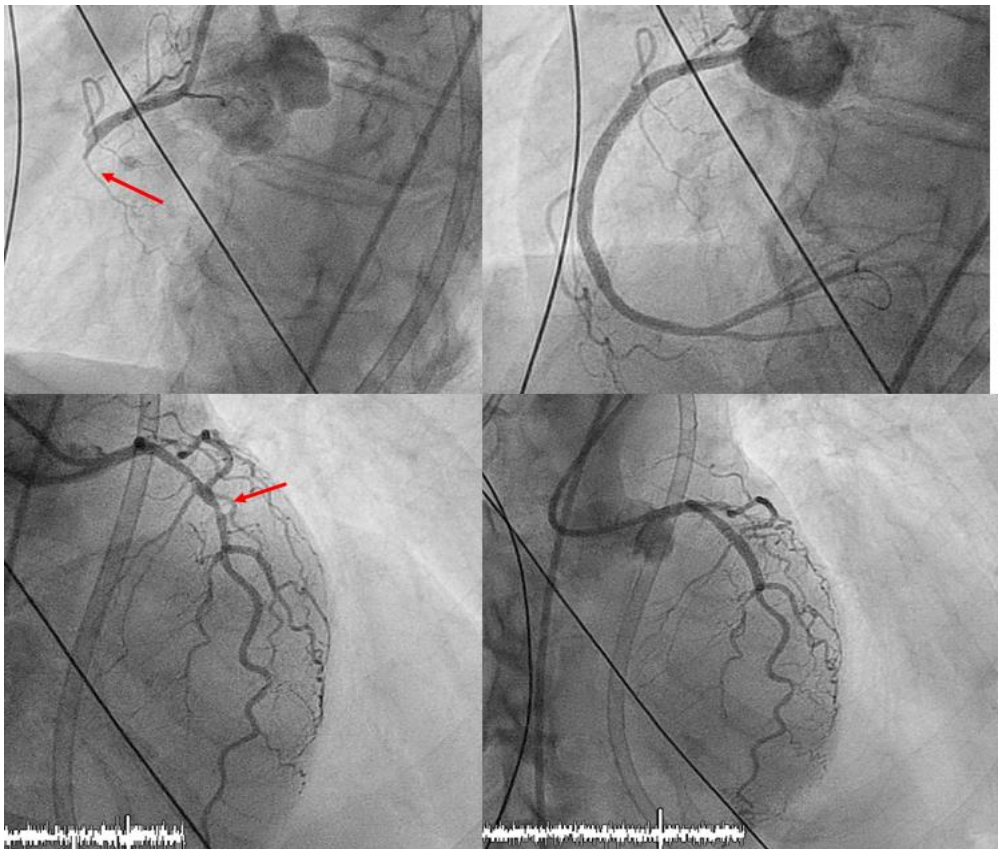

Figure 4: Patient with infarct-related CS with multivessel disease.
Coronary angiography images show total occlusion of the right coronary artery (red arrow, upper left panel) and a high-grade stenosis of the left anterior descending coronary artery (red arrow, lower left panel). On the right panels, successful PCI and stenting of the culprit-lesion (right coronary artery) and the high-grade stenosis of the left coronary artery can be seen.

2.1.4.4 Invasive Haemodynamic Monitoring

An arterial line placement is necessary in all patients with CS to maintain a continuous direct blood pressure monitoring and to obtain frequent blood samples [23]. Invasive haemodynamic

monitoring, e.g. with a Swan-Ganz catheter, is a useful method to exclude other causes of shock. CS haemodynamic parameters are a PCWP >15 mmHg and a cardiac index <2.2 L/min/m^2 [24, 30]. Isolated right ventricular infarction can be indicated by high right-sided filling pressures in the absence of an elevated PCWP.

PiCCO (Pulse Contour Cardiac Output) is a useful method to ensure a continuous haemodynamic monitoring using a femoral or axillary artery catheter and a central venous catheter. In cases where more than one cause of a shock is suspected (e.g. combined septic shock and CS), PiCCO can be a very useful method for diagnosis confirmation by calculating several parameters such as CO, stroke and extravascular volume and for guidance of therapy [31].

2.1.5 Treatment and Management

CS is a life-threatening situation, with the need of immediate initiation of pharmacologic therapy to maintain blood pressure and CO. Mostly the patient with CS needs an admission to the intensive care unit (ICU), which may require the initiation of vasopressors, and inotropes plus additional therapy to prevent the occurrence of MODS.

2.1.5.1 Pharmacological Therapy

Pharmacological therapy in infarct-related CS aims to improve organ perfusion by increasing cardiac output and blood pressure. Generally, all patients presenting with ACS induced CS receive aspirin, which has proven to be effective in reducing mortality [5, 32]. Other oral P2Y12-inhibitors are indicated in addition to aspirin in all patients who undergo PCI [33]. However, most CS patients are intubated and have impaired enteral absorption with consequently reduced bioavailability of these medications [2]. Therefore, intravenous medications like GP IIb/IIIa receptor antagonists may play an important role in CS patients.

Around 90% of CS patients require catecholamines to maintain an adequate organ perfusion pressure [11]. In general, catecholamines aid to maintain adequate blood pressure and help to maintain an adequate flow to the body's organ. The MAP needed for effective splanchnic

and renal perfusion is 65 or 70 mmHg. In patients with reduced tissue perfusion, initiation of inotropic and/or vasopressor drug therapy after assessing the intravascular volume may be necessary.

There is no significant evidence from randomized trials comparing catecholamines in CS [2]. According to a subgroup analysis from the SOAP II (*Sepsis Occurrence in Acutely Ill Patients*) study, dopamine was shown to increase 28-day mortality in comparison to norepinephrine in CS patients [34]. Consequently, the European STEMI guideline and the German–Austrian CS guideline prefer norepinephrine over dopamine when blood pressure is low [35].

Dobutamine is the initial therapy for patients with predominant low cardiac output [35]. The use of levosimendan and its clinical evidence in CS are limited. Initial positive effects in small trials did not translate into a survival benefit in larger clinical trials. In view of its vasodilatory effects with subsequent blood pressure lowering, levosimendan is not a drug of first choice in CS. There are, however, some clinical observations indicating that levosimendan can improve haemodynamics in CS when combined with catecholamines to maintain adequate perfusion pressures. Its current role in CS needs to be defined in further studies [36].

Phosphodiesterase III inhibitors are not recommended in infarct-related CS patients. The TRIUMPH (*The Tilarginine Acetate Injection in a Randomized International Study in Unstable Acute Myocardial Infarction Patients with Cardiogenic Shock*) trial did not show a mortality benefit in the tilarginine arm in addition to early revascularization in both groups [37].

In general, catecholamines cause vasoconstriction and increase the consumption of myocardial oxygen, which may lead to impaired tissue perfusion. Therefore, their use should be restricted to the lowest possible dose and duration [2].

2.1.5.2 Mechanical Support

The use of active mechanical circulatory support (MCS) appears to be a promising therapeutic concept to improve cardiac output while avoiding the possible cardiotoxicity of catecholamines. Passive IABP has been the most widely used device for MCS for the last decades. The main role of the IABP is to increase the CO and coronary perfusion by

decreasing the cardiac afterload and increasing the diastolic coronary perfusion pressure (Figure 5). Depending on the neutral results of the IABP-SHOCK II trial, the routine use of IABP in CS has changed and was consequently downgraded in the new STEMI ESC guidelines to a class IIIB recommendation [35].

The lack of efficacy of IABP led to an increased use of more potent active MCS devices. Among the currently available percutaneous devices left atrial-to-femoral artery MCS such as the TandemHeart™ (TandemHeart, Cardiac Assist, Pittsburgh, PA, USA), axial flow MCS from the Impella® family (Impella 2.5 and Impella CP, Abiomed Europe, Aachen, Germany) and extracorporeal membrane oxygenation (ECMO) are predominantly used for short-term support (Figure 5). These devices improve cardiac function and assure a complete short-term haemodynamic support by reducing cardiac preload, increase of the myocardial blood flow and lactate extraction [2]. However, further studies are needed to define the role of MCS devices in CS.

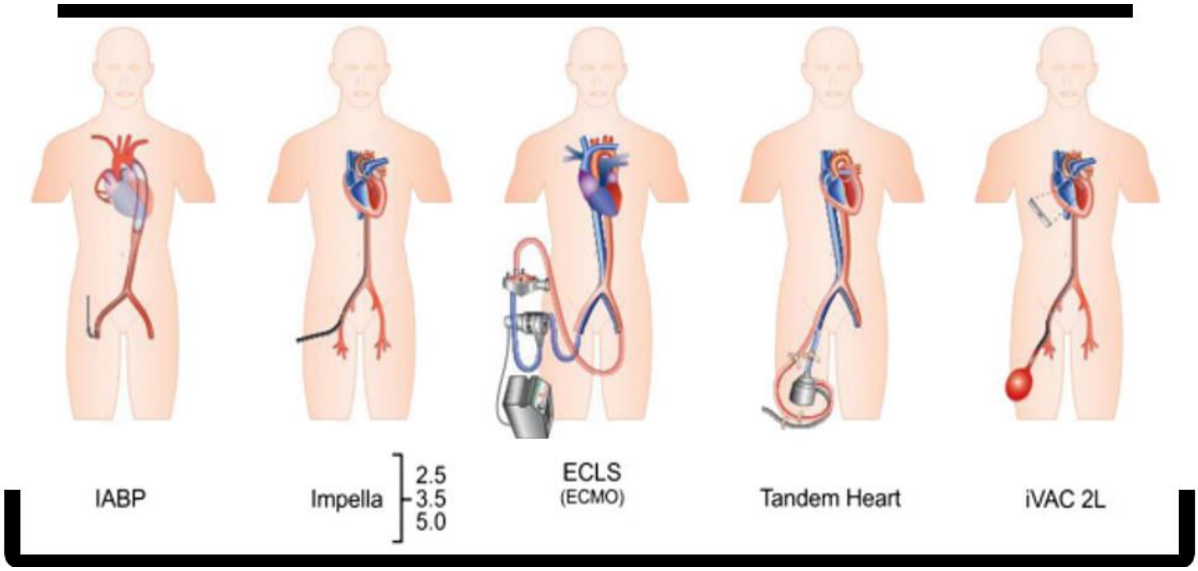

Figure 5: Current percutaneous mechanical support devices for CS: intraaortic balloon pump (A), Impella (B), TandemHeartTM, (C) extracorporeal life support, (D) iVAC 2Lw. Adapted from [2].

2.1.5.3 Revascularization

One of the most important strategies in managing patients with infarct-related CS is early revascularization. Restoring the blood flow in the culprit lesion improves the heart muscle function and reduces the mortality following AMI. According to the SHOCK trial, early

revascularization showed a significant superiority of revascularization over optimal medical management in reducing mortality (50.3% vs 63.1% after 6 months) [4]. Based on the SHOCK trial results and current data, early angiography and revascularization procedures by either PCI or coronary artery bypass grafting (CABG) should be done rapidly in infarct-related CS patients (Class IB recommendation) (Figure 6) [2].

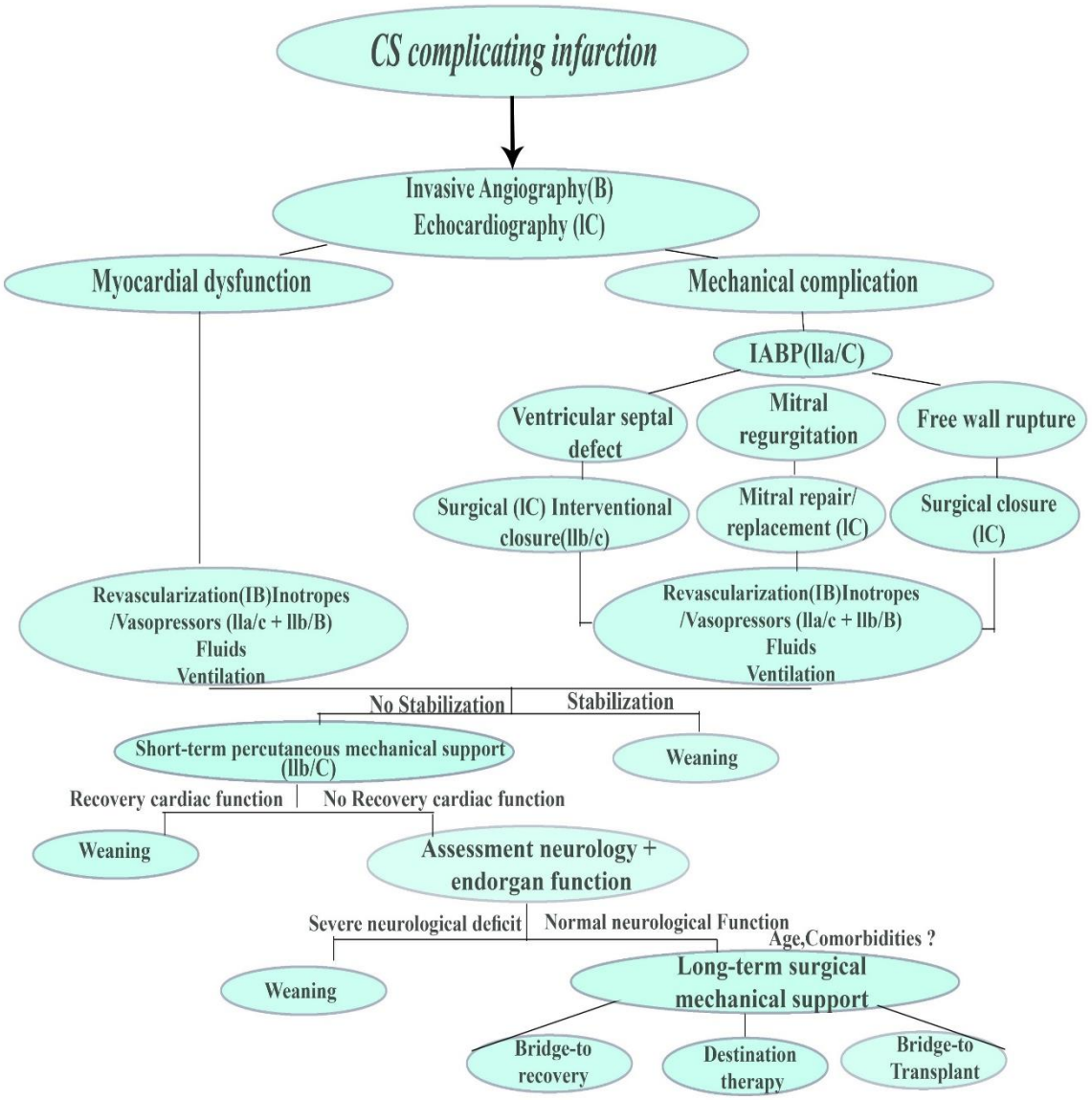

Figure 6: Treatment algorithm for patients with CS complicating AMI. The class of recommendation and level of evidence according to ESC guidelines is provided if available. Adapted from [2].

2.1.6 Prognosis

In the setting of AMI, CS is the leading cause of mortality, which can reach 70 to 90% in the absence of appropriate treatment [23]. In patients with CS, the overall in-hospital mortality rate is 57%. For patients older than 75 years, the mortality rate is 64%, for those younger than 75 years, the mortality rate is 39% [38].

In the GUSTO-I trial, the following predictors of mortality were determined [39]: Previous MI, advanced age, altered sensorium, cold, clammy skin and oliguria

Echocardiography findings such as right ventricular dilation may suggest worse prognosis in CS patients [9]. Moreover, LVEF and mitral regurgitation are considered independent indicators of mortality. For example, reduced LVEF of less than 28% correlates with a 1-year survival rate of 24%, while a higher LVEF is associated with a survival rate of 56%. The absence of mitral regurgitation was observed to be associated with a survival rate of 58% at 1 year, while moderate to severe regurgitation was associated with a 1-year survival of 31% [30].

As demonstrated by the landmark SHOCK trial, outcomes in CS significantly improve when urgent revascularization can be performed [4]. The mortality rates reach 70%, when rapid revascularization is not performed. The procedure type also plays an important role for mortality in CS (e.g. PCI, stent placement, thrombolytic therapy) [23].

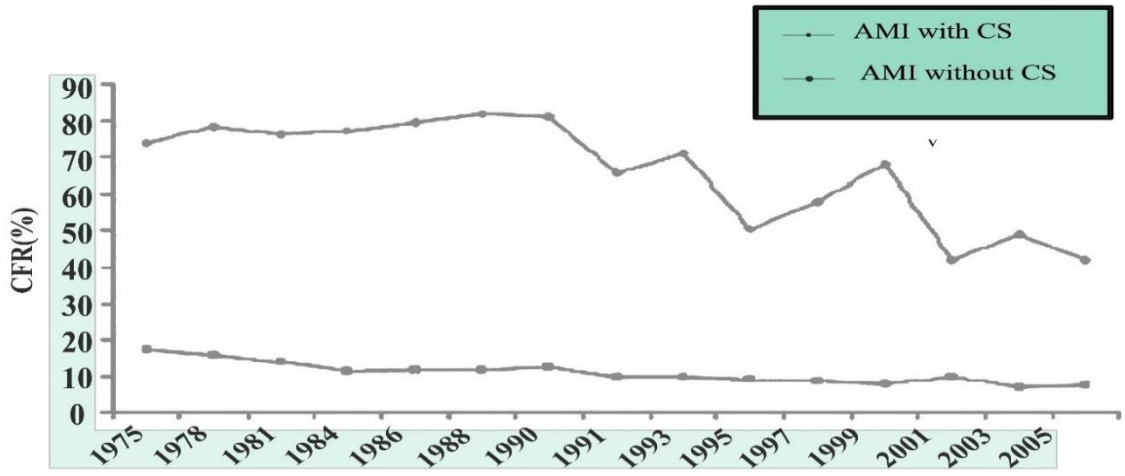

Figure 7: Trend in hospital case-fatality rates in patients with AMI according to presence of CS. Adapted from [16].

CFR=case fatality rate.

2.2 Glycoprotein IIb/IIIa Receptor Antagonists

Antiplatelet drugs are one of the most important therapeutic advances in cardiovascular medicine. GP IIb/IIIa receptor antagonists are promising in CS because of the rapid onset of action and improved bioavailability in comparison to other oral antiplatelets in the setting of CS [2]. GP IIb/IIIa receptors are presented on the platelets surface and count around 50-60 thousand per platelet. They are responsible for the final step of platelet aggregation, which plays a major role in acute vessel closure during ACS. GP IIb/IIIa receptors are a subclass from Integrin with specificity for binding to fibrinogen that reduce thrombus formation by blocking the key binding sites, which are necessary in stabilizing the platelet aggregation pathway [40].

2.2.1 Overview of Thrombus Formation

The coagulation process usually starts after endothelium injury. This injury leads to platelet activation (primary haemostasis) and the exposure of the tissue factor to plasma factor VII, which finally forms the fibrin clot (secondary haemostasis) [41].

The platelet activation process in primary haemostasis can be interrupted by many antiplatelet drugs. These drugs inhibit the activation process reversibly or irreversibly resulting in decreased platelets adherent to each other [42] (Figure 8).

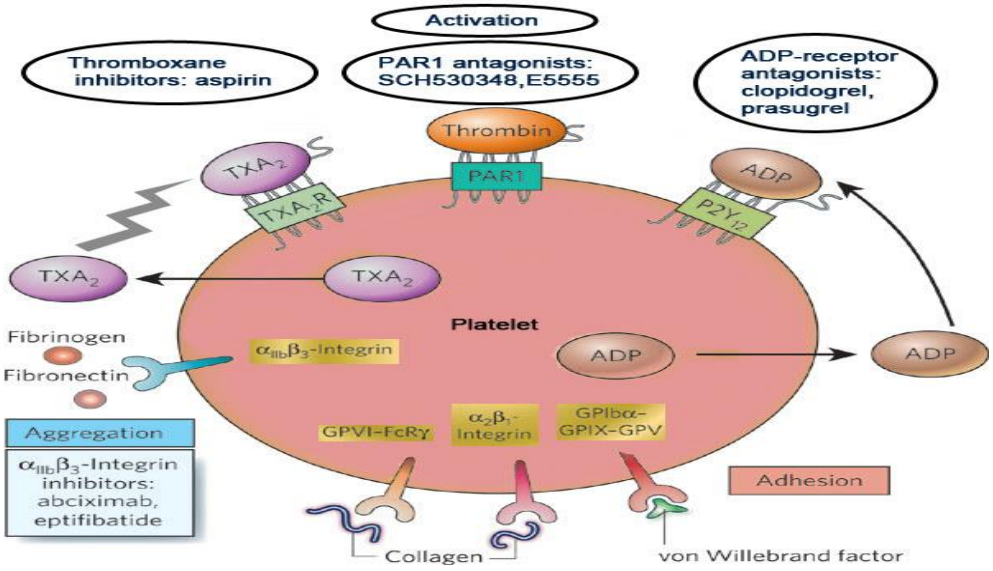

Figure 8: Platelets activation and mechanisms of action of antiplatelet agents. Adapted from [42].
PAR: protease activated receptor; **TxA2**: thromboxane A2.

2.2.2 Classification of GP IIb/IIIa Receptor Antagonists

Naturally occurring peptide inhibitors are not used clinically (examples are a) Trigramin, b) Barbourin, c) Kistrin). The clinically used synthetic inhibitors include three types which are described in detail below (Table 2).

Table 2: Characteristics of GP IIb/IIIa receptor antagonists. Adapted from [43].

	Abciximab	**Eptifibatide**	**Tirofiban**
Type	Antibody fragment	Peptide	Non-Peptide
Platelet bound half-life	Long (h)	Short (sec)	Short (sec)
Plasma half-life	Short (min)	Extended (2h)	Extended (2h)
Return of platelet function (h) *	12	4	4
Reversible with platelet platelet function	Yes	No	No
*50% reduction in antiplatelet effect without transfusion			

2.2.2.1 Monoclonal Antibodies

Abciximab

Abciximab is available since 1995 under the brand name of ReoPro®. It was the first used GP IIb/IIIa receptor antagonist in coronary angioplasty [44]. It is a human-murine chimeric monoclonal antibody fragment (C7E 3 Fab), a large molecule with low dissociation constant blocking the GP IIb/IIIa moiety. It binds to the vitronectin receptor, which is responsible for cell adhesion, migration, and proliferation, thereby inhibiting the thrombus formation [44].

Abciximab has a plasma half-life of about 10 minutes, and a second phase half-life of about 30 minutes. It has a strong binding affinity for GP IIb/IIIa receptors and a low dissociation constant [45]. Due to this, the speed of reversibility is slow (>48 hours) due to prolonged binding to platelets.

2.2.2.2 Peptide Inhibitors

Eptifibatide

Eptifibatide (INTEGRILIN®) is one of the most commonly used GP IIa/IIIb receptor antagonists in clinical routine. The mechanism of action of this drug is that it prevents the binding of fibrinogen, von Willebrand Factor, and other adhesive ligands to the platelet GP IIb/IIIa

receptors by reversibly binding to this complex. Thereby it inhibits the final pathway of platelet aggregation and clot formation [46]. Eptifibatide has a half-life approximately of about 2.5 hours. It rapidly dissociates from its receptor (within 2-4 hours) after the cessation of the therapy and is mainly used to reduce acute cardiac ischaemic events in ACS patients undergoing PCI [47].

2.2.2.3 Non-peptide Inhibitors

Tirofiban

It is available as Aggrastat® since 1998. It is a tyrosine derivative non-peptide mimetic with a half-life of 2.0-2.5 hours [44]. It is short-acting and consequently both bleeding time and platelet aggregation returns back to its normal within 3–8 hours after discontinuing tirofiban infusion [48]. It can be used as an adjunct to heparin and aspirin for treating patients with ACS and coronary angioplasty.

2.2.3 Bleeding and Contraindications of GP IIb/IIIa Receptor Antagonists

Early GP IIb/IIIa receptor antagonist's trials showed high bleeding rates after the use of this strong antiplatelet medication during PCI. For example, in the EPIC (*The Evaluation of 7E3 for the Prevention of Ischaemic Complications*) trial, the major bleeding rate associated with abciximab was 14%. However, through modification in procedural techniques and adjunctive anticoagulant management, the bleeding rate was markedly decreased e.g. with 1% in EPISTENT (*Evaluation of Platelet IIb/IIIa Inhibition in Stenting*) trial [49]. In the setting of life threatening bleeding, discontinuation of GP IIa/IIIb receptor antagonist infusion and platelet transfusion may be required to stop bleeding. Platelet transfusion may not be required with rapidly reversible agents like eptifibatide and tirofiban [50]. Thrombocytopenia has been also observed in rare cases of patients receiving GP IIa/IIIb receptor antagonist. Abciximab-induced thrombocytopenia usually occurs rapidly after administration but may also occur up to 16 days after initial administration [51]. In patients with serious thrombocytopenia and

bleeding transfusion of platelets should be performed. Contraindications for the administration of GP IIb/IIIa receptor antagonists are listed in Table 3.

Table 3: Major GP IIb/IIIa contraindications. Adapted from [50].

Major GP IIb/IIIa receptor antagonist contraindications
Active internal bleeding
Recent (within six weeks) gastrointestinal or genitourinary bleeding of clinical significance.
History of cerebrovascular accident (CVA) within two years, or CVA with a significant residual neurological deficit
Bleeding diathesis
Hypersensitivity to GP IIb/IIIa receptor antagonists
Intracranial neoplasm, arteriovenous malformation, or aneurysm
Recent (within six weeks) major surgery or trauma

3. Methods

This study is a predefined retrospective substudy from the IABP-SHOCK II trial, a multicenter, open label, randomized study performed in 37 centers in Germany. In the IABP-SHOCK II trial, patients with CS complicating AMI undergoing early revascularization therapy were randomized in a 1:1 fashion to either IABP support or to a control group. All patients underwent cardiac catheterization immediately after hospital admission. The revascularization mode (primary PCI of the target lesion only, staged PCI, or CABG) and the choice of stent (bare-metal or drug-eluting stent) was left to the discretion of the operator. The use of thrombectomy was strongly recommended in both groups, in particular, in lesions with high thrombus burden. In resuscitated patients, cooling was initiated after PCI.

In the current GP IIb/IIIa receptors antagonists IABP-SHOCK II substudy the patients were divided into two groups according to the treatment with (n=276) versus without (n=299) GP IIb/IIIa receptor antagonist use. The study was conducted according to the Declaration of Helsinki, has been approved by the local ethics committee, and all patients or their legal representatives gave written informed consent.

3.1 Inclusion Criteria

For study inclusion the patients needed to fulfil the following criteria:

AMI (STEMI or NSTEMI) plus obligatory

1) Planned revascularization (PCI or alternatively CABG);
2) Systolic blood pressure <90 mmHg for >30 minutes or catecholamines required to maintain pressure >90 mmHg during systole plus clinical signs of pulmonary congestion; and
3) Signs of impaired organ perfusion with at least 1 of the following criteria:

a. Altered mental status;

b. Cold, clammy skin and extremities;

c. Oliguria with urine output <30 mL/h; and

d. Arterial lactate >2.0 mmol/L.

3.2 Exclusion Criteria

The exclusion criteria reflect the typical contraindications for inclusion in CS trials and those for the use of IABP. The main exclusion criteria were defined as follows:

- Cardiopulmonary resuscitation longer than 30 minutes
- Absence of intrinsic heart action
- Coma with fixed pupils dilatation not induced by drugs
- Mechanical cause of CS
- Screening 12 hours after the onset of shock
- Massive pulmonary embolism
- Difficulty of IABP insertion by severe peripheral arterial disease
- Aortic insufficiency more than grade II in severity
- Older than 90 years
- Shock as a result of a condition other than AMI
- Life expectancy of less than 6 months as a result from severe concomitant disease
- Early mortality, i.e. patient death before or during the intervention

3.3 Clinical Endpoint

The primary study endpoint of this subanalysis was one-year mortality with respect to the treatment with versus without GP IIb/IIIa inhibitors. The secondary endpoint of the study was 30-day mortality.

Safety endpoints were:

- Severe and moderate bleeding during the hospital stay assessed according to the GUSTO criteria.
- Stroke, identified by the presence of new neurologic symptoms, and confirmed by ischaemia or bleeding signs on computed tomography.
- Recurrent AMI using the universal definition of myocardial infarction [27].

3.4 Statistical Analysis

As most continuous variables were not normally distributed, all continuous variables are presented as medians with interquartile range (IQR) for reasons of uniformity. Categorical data are presented as counts or proportions with the corresponding percentages. For comparison of continuous variables, student's t-test or Mann-Whitney test were used, for comparison of categorical variables Fisher´s exact- or Chi^2-test were used, as appropriate.

Kaplan-Meier analysis with log-rank-testing and corresponding hazard ratios (HR) was used for outcome assessment. In addition, a multivariate Cox model with forward selection was used to test for independent predictors of one-year mortality. The variables for each model were selected by univariately comparing demographic variables (age, gender), risk factors, medical history, chronic medication and lab parameters from the time of hospital admission between patients with event vs. event-free patients. All variables with a p-value <0.1 from this univariate comparison were entered into the Cox regression model (first model), from which the final model was selected by forward selection (with entry level $p<0.05$).

The outcome analysis was performed by intention to treat. The time of survival was calculated from randomization to the time of death or last known follow-up. The expected survival curves were adjusted for the significant covariates from the Cox proportional hazard model.

Statistical analysis was performed using commercially available software (SPSS version 20.0). A two-tailed p-value <0.05 was considered statistically significant.

4. Results

Between June 2009 and March 2012, 575 patients of 600 initially randomised patients had available information regarding the administration of GP IIb/IIIa receptor antagonists and were included in the study. Of these, 276 patients received GP IIb/IIIa receptor antagonists (group A: GP IIb/IIIa receptor antagonists group), whereas 299 patients did not receive GP IIb/IIIa receptor antagonists (group B: non GP IIb/IIIa receptor antagonists group).

4.1 Patient Characteristics

Baseline clinical and angiographic characteristics of the two patient groups are illustrated in Table 4. Patients with GP IIb/IIIa receptor antagonist application were significantly younger (p<0.01), had a lower incidence of diabetes mellitus (p<0.05) and presented significantly more often with STEMI (p<0.001).

Table 4: Baseline clinical and angiographic characteristics. Values are median (interquartile range) or n/N (%). **BMI:** body mass Index. **PAD**: peripheral artery disease. **PCI:** percutaneous coronary intervention. **CABG:** coronary artery bypass grafting. **CPR:** cardiopulmonary resuscitation. **CAD:** coronary artery disease. **RCA:** right coronary artery. **LAD:** left anterior descending. **LCX:** left circumflex. **LVEF:** left ventricular ejection fraction.

	GP IIb/IIIa-receptor antagonists	No GP IIb/IIIa-receptor antagonists	P-value
Number of patients	276 (48%)	299 (52%)	
Age, years	67 (57- 74)	70 (59-78)	< 0.01
Male	72.1% (199/276)	65.9% (197/299)	0.11
BMI, kg/m^2	27.34 (24.69-29.40)	27.45 (24.69-30.67)	0.30
Cardiovascular risk factors			
- Smoking	38% (103/271)	32.9% (98/298)	0.20
- Hypertension	69.2% (189/273)	68.4% (203/297)	0.82
- Dyslipidaemia	35.7% (97/272)	39.4% (117/297)	0.36
- Diabetes mellitus	27.8% (76/273)	36.2% (108/298)	< 0.05
Previous MI	19.9% (55/276)	23.2% (69/298)	0.35

Previous Stroke	6.2% (17/276)	7.4% (22/298)	0.56
PAD	10.9% (30/276)	12.8% (38/298)	0.49
Previous PCI	18.9% (52/275)	20.1% (60/298)	0.71
Previous CABG	4.7% (13/276)	5.7% (17/298)	0.59
Cold, pale skin or extremities	85.5% (235/275)	81.6% (244/299)	0.22
Oliguria (≤ 20 ml/h)	30.9% (85/275)	30.4% (91/299)	0.90
Arterial lactate > 2 mmol/l	73.8% (203/275)	74.2% (222/299)	0.91
Thrombolysis < 24h	5.1% (14/276)	11.0% (33/299)	< 0.01
CPR	44.9% (124/276)	44.1% (132/299)	0.85
ST-elevation	74.3% (202/272)	53.0% (158/298)	< 0.001
Systolic blood pressure (mmHg)	86 (79-101)	91 (80-110)	< 0.001
Diastolic blood pressure (mmHg)	57 (48-66)	60 (49-70)	0.23
Heart rate (/min)	96 (80-110)	89 (70-110)	< 0.05
Mean blood pressure (mmHg)	67 (57-77)	70 (60-83)	< 0.05
Serum creatinine (mg/dl)	1.23 (1.02-1.59)	1.33 (1.07-1.73)	0.09
Creatinine clearance (ml/min)	64.93 (45.14-84.82)	55.56 (38.94-78.75)	< 0.05
CAD: stenosis ≥ 50%	100% (275/275)	97% (290/299)	< 0.01
- 1-vessel-CAD	20.4% (56/275)	2.8% (69/290)	0.33
- 2-vessel-CAD	27.6% (76/275)	25.5% (74/290)	0.57
- 3-vessel-CAD	52% (143/275)	50.7% (147/290)	0.76
No CAD	0% (0/275)	3% (9/299)	< 0.01
Culprit-Lesion			
- Left main	10.2% (28/275)	7.3% (21/289)	0.22
- RCA	20.7% (57/275)	30.8% (89/289)	< 0.01
- LAD	49.5% (136/275)	38.4% (111/289)	< 0.01
- LCX	16.4% (45/275)	21.1% (61/289)	0.15
- Bypass	3.3% (9/275)	1.7% (5/290)	0.24
LVEF (%)	35 (25-45)	35 (25-45)	0.51

4.2 Procedural and Treatment Characteristics

Early revascularization was performed in almost all patients with primary PCI (99%). Procedural and treatment characteristics are shown in Table 5. Patients in the GP IIb/IIIa group had a significantly impaired TIMI-flow 0 in the infarct-related artery prior PCI (65% versus 55%, p<0.05). After PCI, there was no difference in TIMI-flow between groups. There were also no differences between groups in the type or number of used stents. Hypothermia was performed equally often in both groups.

Table 5: Procedural and treatment characteristics.
PCI: percutaneous coronary intervention. **CABG:** coronary artery bypass grafting. **ACE:** angiotensin converting enzyme. **TIMI:** thrombolysis in Myocardial Infarction. **ICU:** intensive care unit. **UF:** unfractionated. **LMW:** low molecular weight.

	GP IIb/IIIa-receptor antagonists	No GP IIb/IIIa-receptor antagonists	P-value
Number of patients	276 (48%)	299 (52%)	
Primary – PCI	98.9% (273/276)	93.3% (279/299)	< 0.001
Stents	95.2% (260/273)	93.5% (260/278)	0.38
Bare-metal-Stent	53.5% (139/260)	58.5% (152/260)	0.25
Drug-eluting-Stent	48.8% (127/260)	45.0% (117/260)	0.38
Thrombectomy device before / after PCI	38% (105/276)	17.7% (53/299)	< 0.0001
TIMI-flow before PCI			
- TIMI-flow before PCI grade 0	65.4% (178/272)	55.2% (154/279)	< 0.05
- TIMI-flow before PCI grade 1	8.8% (24/272)	15.8% (44/279)	< 0.05
- TIMI-flow before PCI grade 2	14.7% (40/272)	12.9% (36/279)	0.54
- TIMI-flow before PCI grade 3	11.0% (30/272)	16.1% (45/279)	0.08
TIMI-flow after PCI			
- TIMI-flow after PCI grade 0	2.9% (8/272)	5.7% (16/279)	0.11
- TIMI-flow after PCI grade 1	4.0% (11/272)	3.2% (9/279)	0.61
- TIMI-flow after PCI grade 2	11.8% (32/272)	5.4% (15/279)	< 0.01

- TIMI-flow after PCI grade 3	81.3% (221/272)	85.7% (239/279)	0.16
Emergency CABG	2.2% (6/273)	1.1% (3/279)	0.30
CABG in interval	1.1% (3/273)	1.1% (3/279)	0.98
IABP implantation	51.8% (143/276)	55.2% (165/299)	0.42
Assist devices	4.3% (12/276)	3.0% (9/299)	0.39
Mild hypothermia	34.4% (95/276)	33.4% (100/299)	0.81
Mechanical ventilation	74.6% (206/276)	78.6% (235/299)	0.26
ICU	6 (3-12)	7 (3-14)	0.35
Renal replacement therapy	4.3% (12/276)	6% (18/299)	0.37
Acute medications			
- Aspirin	93.8% (259/276)	89.6% (268/299)	0.07
- Clopidogrel	64.9% (179/276)	69.6% (208/299)	0.23
- Prasugrel	22.1% (61/276)	14.4% (43/299)	< 0.05
- Ticagrelor	4.2% (8/191)	5.6% (13/232)	0.50
- UF Heparin	94.6% (261/276)	89.6% (268/299)	< 0.05
- LMW Heparin	3.6% (10/276)	3.3% (10/299)	0.86
- Bivalirudin	10.9% (30/276)	11.4% (34/299)	0.85
- GP IIb/IIIa-receptor antagonists	100% (276/276)	0% (0/299)	
Medication at discharge/death			
- Statin	75.9% (202/266)	70.8% (204/288)	0.17
- Aldosterone antagonists	28% (74/264)	19.2% (55/287)	< 0.05
- Beta-blocker	66.4% (174/262)	62.8% (181/288)	0.38
- ACE inhibitor / Angiotensin II inhibitor	65.9% (174/264)	58.3% (168/288)	0.07
- Catecholamine duration, days	3 (1-5)	3 (1-6)	0.48
Days until final haemodynamic stability	3 (1-6)	3 (1-6)	0.83

4.3. Clinical Outcome

The clinical outcome after one month (secondary endpoint) is shown in Table 6. There were no differences between the groups in early mortality (p=0.29) or in the predefined safety endpoints (stroke, bleeding, MI) after 30 days.

Table 6: One-month clinical outcome.
MI: myocardial infarction

	GP IIb/IIIa-receptor antagonists	No GP IIb/IIIa-receptor antagonists	P-value
Number of Patients	276 (48%)	299 (52%)	
Death (30 days)	35.9% (99/276)	40.1% (120/299)	0.29
MI (30 days, survivors)	4.0% (7/177)	1.7% (3/179)	0.19
Stroke (30 days, survivors)	0.6% (1/177)	1.1% (2/179)	0.57
Bleeding (30 days, survivors)	18.1% (32/177)	21.2% (38/179)	0.45
Moderate bleeding (30 days, survivors)	16.4% (29/177)	20.1% (36/179)	0.36
Major bleeding (30 days, survivors)	2.8% (5/177)	1.7% (3/179)	0.46
In-hospital events			
- Stent thrombosis, in-hospital	1.1% (2/177)	0.6% (1/179)	0.56
- Peripheral ischaemic vascular complication requiring intervention, in-hospital	2.8% (5/177)	2.2% (4/179)	0.72
- Sepsis, in-hospital	16.9% (30/177)	19.6% (35/179)	0.52

However, after one year there was a significant unadjusted decrease in mortality in the GP IIb/IIIa receptor antagonists group (48% vs. 52% p<0.05, Table 7, Figure 9). After adjustment for age and other important prognostic markers, the application of GP IIb/IIIa receptor antagonists was no longer an independent predictor of mortality in Cox proportional hazard analysis (HR 0.93, confidence interval 0.73 to 1.18) (Table 8). Regarding safety, there were no differences in bleeding or stroke after one year (Table 7).

Table 7: One-year clinical outcome.

	GP IIb/IIIa-receptor antagonists	No GP IIb/IIIa-receptor antagonists	P-value
Number of patients	276 (48%)	299 (52%)	
Death (365 days)	44.6% (123/276)	53.2% (159/299)	< 0.05
MI (365 days, survivors)	8.5% (13/153)	3.6% (5/140)	0.08
Stroke (365 days, survivors)	2.6% (4/153)	0.7% (1/140)	0.21
Bleeding (365 days, survivors)	18.9% (29/153)	19.3% (27/140)	0.94
Moderate bleeding (365 days, survivors)	18.1% (50/276)	19.7% (59/299)	0.62
Major bleeding (365 days, survivors)	3.9% (6/153)	1.4% (2/140)	0.19

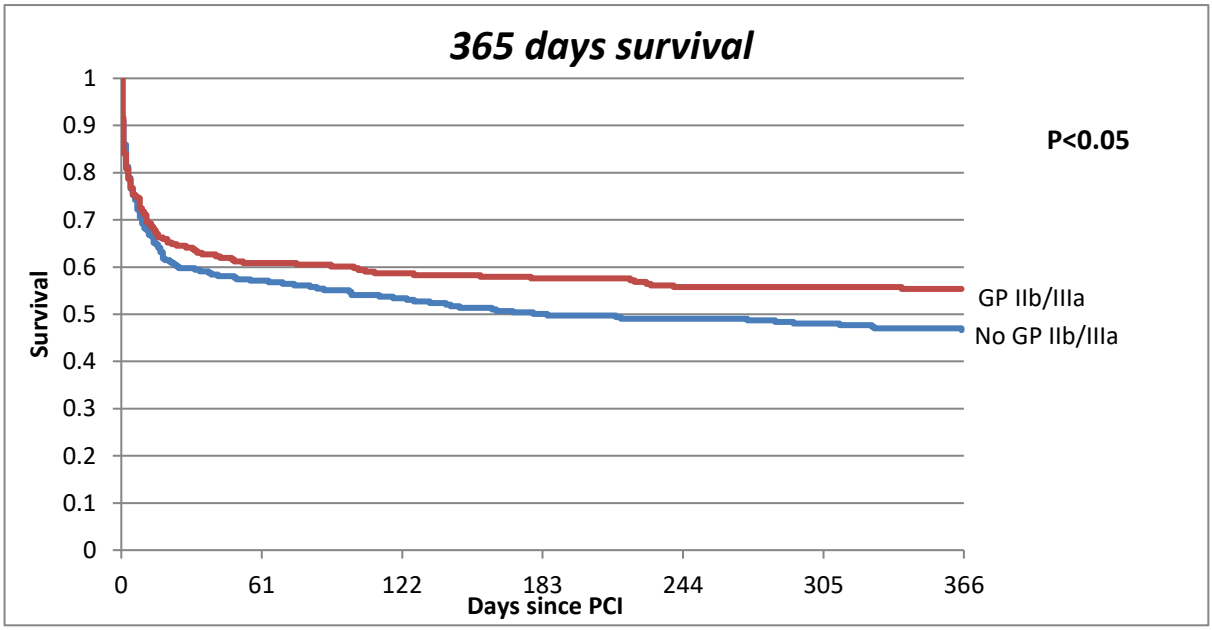

Figure 9: Unadjusted one-year survival
Unadjusted one-year survival curve during one-year follow-up in patients treated with GP IIb/IIIa receptor antagonists (red line) versus no GP IIb/IIIa receptor antagonists (blue line).

Table 8: Cox regression analysis for prediction of mortality at 1 year follow-up.

	Hazard Ratio	95% Hazard Ratio Confidence Limits		P Value
GP IIb/IIIa receptor antagonists	0.863	0.675	1.104	0.2406
Age (years)	1.296	1.139	1.414	<0.0001
Previous stroke	1.749	1.178	2.598	0.0056
PH < 7.36	1.397	1.047	1.8664	0.0232
Oliguria	1.341	1.038	1.733	0.0246
Serum creatinine (mmol/l)	1.002	1.001	1.004	0.0002
Lactate >2 (mmol/l)	1.645	1.166	2.322	0.0046

5. Discussion

This post hoc IABP-SHOCK II trial subanalysis represents the first large analysis of the efficacy and safety of GP IIb/IIIa receptor antagonists in patients with infarct-related CS undergoing temporary PCI with contemporary revascularization techniques. The major findings are as follows:

1) In the setting of infarct-related CS, GP IIb/IIIa receptor antagonist application results in an unadjusted mortality reduction after one-year.
2) Multivariate adjustment revealed that the observed mortality differences were likely related to differences in baseline risk and clinical characteristics.
3) Regarding safety there was no differences in bleeding or stroke between the groups at one year.

5.1 Role of GP IIb/IIIa Receptor Antagonists in Coronary Artery Disease

Most of the trials in ACS, which showed superiority of GP IIb/IIIa receptor antagonists over placebo in mortality reduction, were performed before the routine use of P2Y12 inhibitors. Evidence supporting the use of abciximab in patients with STEMI undergoing primary PCI comes from a meta-analysis of over 27,000 patients included in 11 trials. Compared to placebo, this meta-analysis showed that abciximab significantly lowered the rate of death at 30 days (2.4 versus 3.4%; odds ratio 0.68, 95% CI 0.47-0.99) [52]. However, after the advent of routine use of dual antiplatelet therapy data were less consistent. The BRAVE-3 trial showed no benefit of abciximab in acute STEMI patients undergoing PCI who were treated with a loading dose of 600-mg Clopidogrel [53], whereas in the ON-TIME 2 trial, a high-bolus-dose of tirofiban in addition to aspirin, clopidogrel and heparin, showed a significant improvement in clinical outcome in STEMI patients after PCI [54].

Available data from observational studies and small randomized trials show equal efficacy between abciximab, tirofiban, and eptifibatide [55,56]. Accordingly, there is no clear evidence supporting the use of any agent above the other. However, in the setting of primary PCI, abciximab is the best studied GP IIb/IIIa receptor antagonist [57, 58] and may therefore

be chosen because of its proven efficacy in many trials. Others use tirofiban and eptifibatide since those provide similar efficacy but at lower costs [59].

According to current guidelines, it is not recommended to routinely use GP IIb/IIIa receptor antagonists for patients undergoing primary PCI, who received two antiplatelet therapies (aspirin and a P2Y12 inhibitor). Some STEMI patients, those with no reflow or large thrombus burden at the time of primary PCI, may benefit from intravenous GP IIb/IIIa receptor antagonists [35]. The current guidelines state that the use of GP IIb/IIIa receptor antagonists in this subset of patients should be considered (Class IIA recommendation) [2, 35].

5.2 Efficacy of GP IIb/IIIa Receptor Antagonists in CS

Due to impaired and delayed onset of action of oral antiplatelets (e.g. Clopidogrel, Ticagrelor, Prasugrel) in CS, intravenous GP IIb/IIIa receptor antagonists may be beneficial in CS [2]. Absorption may also be decreased by the effects of vasopressors and/or opiates, or in patients with liver dysfunction, conditions that are frequently present in patients with CS. In high-risk patients with STEMI, several trials and meta-analysis documented clinical benefits of GP IIb/IIIa receptor antagonists as adjunct to primary PCI [8]. GP IIb/IIIa receptor antagonists have the potential to improve coronary microcirculation and to prevent distal platelet microembolization. Moreover, a lytic effect on platelet-rich thrombi (dethrombosis), and suppression of inflammation as well as reperfusion injury has been described. Furthermore, in the early phase of infarction, a larger platelet composition of the thrombus and the presence of a larger amount of viable myocardium, as compared to a delayed phase, could increase the benefits from GP IIb/IIIa receptor antagonists [60,61]. All of these effects may be important to improve the poor patient prognosis in infarct-related CS.

However, results from prior infarction trials cannot be extrapolated to the specific high-risk cohort of patients with CS. As a result of their high mortality risk and the difficulties of enrolling CS patients in randomized controlled trials, this cohort of patients is an understudied population with respect to optimal antiplatelet treatment. Almost all trials excluded patients

who suffered from CS complicating AMI and there is a lack of data comparing the safety and efficacy of different GP IIb/IIIa receptor antagonists in the setting of CS.

According to current guidelines and experience, a liberal use of GP IIb/IIIa receptors antagonists in CS is recommended, especially in patients with high thrombus burden and slow flow after PCI [2]. However, further studies like the current study from our group are required to conclusively ascertain the role of GP IIb/IIIa receptor antagonists in CS.

The data presented here are novel in this respect, as only small studies and mainly registries with several limitations assessed the potential of GP IIb/IIIa receptor antagonists to enhance reperfusion success and survival. A cohort from Antoniucci et al. with 77 consecutive CS patients, showed lower mortality rates in the abciximab treated group as compared to the control group without abciximab. Furthermore, abciximab administration was the only independent predictor of 1-month mortality in this study [62]. However, the small number of patients, the younger age in the abciximab group and the bias in patients with versus without abciximab administration are limitations of this study.

The effect of eptifibatide in patients with CS was evaluated in a post-hoc subgroup analysis from the PURSUIT trial [9]. In this study, the incidence of death at 30 days was significantly reduced by using eptifibatide (48% versus 58% in patients without AMI and 69% versus 85% in patients with AMI). However, this study was a non-randomized retrospective analysis, and the shock status was an outcome rather than a baseline and/or inclusion variable.

More recently, the only randomized multicenter PRAGUE-7 trial studied GP IIb/IIIa receptor antagonists in CS. The primary endpoint of PRAGUE-7 was a 30-day combined outcome of death, reinfarction, stroke and new renal failure. This trial which included 80 CS patients could not show any mortality benefit from routine pre-procedural abciximab when compared with a selective abciximab use during PCI in patients with CS undergoing primary PCI [2,10]. The result of this trial was however inconclusive because of the small number of patients, the 35% crossover between the two groups (abciximab was used in 35% of those in the standard-therapy arm) and the heterogeneous population sample.

Furthermore, the effect of abciximab was evaluated by De Felice and his colleagues. In this registry study 410 patients with STEMI and CS who underwent PCI treated with or without abciximab were included. The primary endpoint of the study was survival at 1-year follow-up. This study found that in patients with STEMI complicated by CS undergoing PCI, abciximab did no show clinical benefits after 1-year follow-up. However, this study was retrospective in nature with again a relatively small number of patients without adequate statistical power to detect differences between the two groups [63].

Our findings expand these findings as we can show in our study a significant unadjusted mortality reduction after one-year (48% vs. 52% $p<0.05$). However, GP IIb/IIIa receptors antagonists were not identified as an independent predictor of survival after 1-year follow-up on Cox regression modelling (Table 9). There were many differences in baseline risk and clinical characteristics between the groups including age, diabetes mellitus, the presence of STEMI and differences in TIMI-flow of the culprit vessel. For illustration, data from observational mainly retrospective studies suggest an association between glucose levels and prognosis of CS patients [64]. In a recently published risk score for CS, glucose levels on admission emerged as one of the strongest predictors of short-term mortality for prognosis and was included as one of the 6 score variables for optimized prognosis estimation in patients with CS [64]. Therefore, the mortality reduction benefits in the GP IIb/IIIa receptors antagonist group were most likely related to these baseline differences between groups.

Regarding predictors of mortality in infarct-related CS, age was already identified as a strong independent predictor of one-year survival in previous studies [7, 63]. Our data support this finding and associated comorbidities may explain the adverse impact of advanced age on survival.

Patients with GP IIb/IIIa receptors antagonist application presented more often with TIMI-flow 0 in the infarcted vessel, which reflects an increased risk in patients with GP IIb/IIIa application. TIMI-flow pre PCI is an important determinant of prognosis and was shown in many trials to be a predictor of mortality [60, 61].

Most trials studied the effect of GP IIb/IIIa receptors antagonist in conjunction with clopidogrel. The additional benefit of GP IIb/IIIa receptors antagonist in the background of new oral antiplatelet drugs (such as ticagrelor and prasugrel) is largely unknown [65]. Consequently, the benefit and safety of adding the potent and prompt platelet inhibitors (i.e. ticagrelor and prasugrel) to GP IIb/IIIa receptor antagonists have not been evaluated yet and require further investigation [65,66]. In the TRITON–TIMI 38 (Improvement in Therapeutic Outcomes by optimizing platelet InhibitioN with Prasugrel Thrombolysis in Myocardial Infarction 38) trial GP IIb/IIIa receptors antagonists were used in 55% of patients. The rates of TIMI major and minor non-CABG bleeding was overall increased. However, this increase did not influence neither the clinical benefit nor the risk of bleeding with prasugrel compared to clopidogrel [65, 67]. Very recently, another subanalysis of the unique IABP-SHOCK II study cohort demonstrated that the use of potent P2Y12 receptor inhibitors like prasugrel or ticagrelor is feasible and might not be harmful in selected patients with CS complicating AMI [68]. However, the superiority in comparison to clopidogrel has not been proven. Furthermore, the ISAR-SHOCK registry demonstrated a lower mortality risk with prasugrel treatment as compared to clopidogrel therapy without increasing the risk of bleeding. These findings, however, need to be confirmation from specifically designed randomised studies in CS patients [69].

Further randomized data is required to evaluate the effect and safety of GP IIb/IIIa receptors antagonist in comparison to the new potent antiplatelets such as ticagrelor and prasugrel. This data is also required to show if there is a role of GP IIb/IIIa receptors antagonist in AMI complicated by CS as an adjunct to the optimal oral antiplatelet loading, newer P2Y12 receptor antagonists, and direct thrombin inhibitors [65, 66].

Cangrelor a novel intravenous $P2Y_{12}$ receptor antagonist may also play a major role in STEMI patients and CS who underwent PCI [70]. Cangrelor is a new antiplatelet agent with a potent effect, rapid onset and offset of action. The clinical efficacy and safety of cangrelor has been evaluated by many trials like the CHAMPION PHOENIX (Cangrelor versus standard therapy to achieve optimal Management of Platelet Inhibition) trial. In this trial 10.900 patients with ACS or stable angina who underwent PCI treated with intravenous cangrelor vs oral

clopidogrel were included. The primary endpoint was 48 hours as well as 30-day combined outcome of death, AMI, ischaemia driven revascularization and stent thrombosis. This trial showed a reduction of the primary endpoint in the intravenous cangrelor group when compared with oral clopidogrel use during PCI (4.7 vs. 5.9 %; p = 0.005) [70]. Most trials studied the effect of cangrelor in conjunction with clopidogrel. The benefit of cangrelor in comparison to the new oral antiplatelet drugs (such as ticagrelor and prasugrel) is still unknown [70].

5.3 Safety of GP IIb/IIIa Receptor Antagonists in CS

CS patients are prone to suffer from bleeding events due to various reasons including their often temporary need for resuscitation requiring repeated chest compression, insertion of a central venous catheter, arterial sheaths and the use of therapeutic anticoagulation. Of note, we did not observe an excess of bleeding complications in the GP IIb/IIIa receptor antagonist group. This observation is in line with previous data from many trials such as ESPRIT [*Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy*] and TARGET [*Do Tirofiban And ReoPro Give Similar Efficacy Trial*]) [71]. Moreover, our work importantly did not show significant differences between the groups in reinfarction or stroke. These findings are also in line with the PRAGUE-7 trial, which also showed no differences in safety between groups [10].

Based on our data and previous observations, the use of GP IIb/IIIa receptors antagonist might not be harmful in CS patients and could be endorsed for antiplatelet treatment of AMI patients complicated by CS and undergoing high risk PCI.

5.4 Clinical relevance of GP IIb/IIIa Receptor Antagonists in CS

In order to gain solid evidence on the safety and efficacy of potent platelet inhibition in CS patients, randomized studies are needed to determine the optimal treatment regimen in patients with AMI complicated by CS undergoing PCI. Because of an unadjusted mortality

reduction and acceptable safety profile, our results of the predefined IABP-SHOCK II trial subgroup may provide a basis for such studies. The intravenously administered GP IIb/IIIa receptor antagonists might be an alternative option in the CS condition, because their treatment efficacy does not require any prior active absorption or in vivo bioactivation. The prompt antiplatelet effect compared to ADP inhibitors, which is also not influenced by patient genotypes [66,71], make GP IIb/IIIa receptor antagonists a valid treatment option in CS.

However, in comparison to other antiplatelets regimens including ticagrelor and prasugrel, it remains unclear if additional GP IIb/IIIa receptor antagonists use is of clinical value [66], especially because of the fact that there have been no randomized studies specifically evaluating the role of GP IIb/IIIa receptors antagonist in the background of newer antiplatelets drugs. Importantly, current guidelines do not recommend the routine use of GP IIb/IIIa receptor antagonists for PCI patients, who received two antiplatelet therapies [59]. But at least it can be stated that GP IIb/IIIa receptors antagonist should be used as an adjunct to the optimal oral antiplatelet loading including newer P2Y12 receptor antagonists, particularly in PCI cases with high thrombus burden and slow flow after PCI, especially in patients with CS.

5.5 Limitations

There are limitations of this study that need to be acknowledged. This analysis is retrospective in nature despite prospective data handling and the number of patients is still only moderate. There was no routine platelet function monitoring of patients, so we were not able to investigate pharmacodynamic effects. Although the differences in patient characteristics highlight a treatment bias between the two groups, a risk-adjusted survival analysis as well as an age specific subgroup analysis were employed to mitigate these limitations.

6. Conclusion

This retrospective subanalysis demonstrates that in the setting of infarct-related CS, GP IIb/IIIa receptor antagonist application results in an unadjusted mortality reduction after one-year. Multivariate adjustment revealed that the observed mortality differences were likely related to differences in baseline risk and clinical characteristics. Further randomized studies are warranted to conclusively ascertain the role of GP IIb/IIIa receptor antagonists in CS.

7. Summary

CS is a medical emergency defined by decreased CO and evidence of critical endorgan hypoperfusion [1,2]. The majority of CS cases are due to AMI, but other less frequent causes include mechanical causes (such as acute mitral regurgitation, ventricular septal), myocarditis or arrhythmias [1,2]. CS is the leading cause of death in AMI, with mortality rates of up to 70-90% in the absence of rapid diagnosis and aggressive care. However, in spite of optimal medical treatment and revascularization strategies, mortality rates of infarct related CS are declining to 40–50% [4]. Nowadays, early restoration of coronary blood flow represents the standard therapy for patients with CS due to AMI, and is the most important intervention for improving survival rates [2]. Although revascularization emerged as an important survival component, restoration of normal epicardial flow by PCI in CS is lower in comparison to non-CS patients [7].

Because of delayed onset of action of oral antiplatelets (e.g. clopidogrel, ticagrelor, prasugrel) in CS, intravenous GP IIb/IIIa receptor antagonists may have an important role for improving survival in CS [2]. Several trials showed clinical benefits of GP IIb/IIIa receptor antagonists as adjunct to primary PCI in high-risk patients with STEMI [8]. However, the role of GP IIb/IIIa receptor antagonists on mortality in patients with infarct-related CS is not conclusively ascertained. The aim of this study was therefore to assess the efficacy and safety of GP IIb/IIIa receptor antagonists in patients with CS as a predefined substudy from the IABP-SHOCK II trial.

In the IABP-SHOCK II trial, patients with CS complicating AMI undergoing early revascularization therapy were randomized to a therapy with versus without IABP support. In our retrospective subanalysis the patients were divided into two groups according to the treatment with (n=276) versus without (n=299) GP IIb/IIIa receptor antagonists. The primary study endpoint was mortality within 1 year after randomization.

Patients with GP IIb/IIIa application were significantly younger (67 [57-74] vs. 70 [50-78], $p<0.01$), presented significantly more often with ST-elevation myocardial infarction (74%

versus 43%, p<0.001) and had significantly more often TIMI-flow 0 in the infarct-related artery prior PCI (65% versus 55%, p<0.05). There were no differences in early mortality after 30 days between groups (36% versus 40%, p=0.29). However, after one year there was a significant unadjusted decrease in mortality in the GP IIb/IIIa inhibitor group (48% vs. 52% p<0.05). After adjustment for age and other important prognostic markers, the application of GP IIb/IIIa receptor antagonists was no longer an independent predictor of mortality in Cox proportional hazard analysis (HR 0.93, confidence interval 0.73 to 1.18). Regarding safety there was no differences in bleeding or stroke between the groups at 30 days and after one year.

In summary, our data demonstrate that treatment with GP IIb/IIIa receptor antagonists in patients with infarct-related CS results in an unadjusted mortality reduction after one-year follow up. After multivariate adjustment, however, the observed mortality differences were likely related to differences in baseline risk and clinical characteristics. To definitively assess the role of GP IIb/IIIa receptor antagonists in CS, larger randomized studies are needed.

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Personal information

Name: Amr Abdin, MD, MRCP(UK)
Date of birth: 12.09.1986 in Syria
Nationality: Syrian
Address: Kahlhorst str.17, 23562 Lübeck, Germany
Tel: +491793864783
E-mail: amr.abdin@gmail.com

Qualifications

12/2017: German specialty certificate in internal medicine and cardiology (Facharzt)
6/2017: ESC Heart Failure Certification
2/2017: Passed the written part of the ESC TTE certificate (logbook submitted)
7/2014: German right to work as a Physician (Deutsche Approbation)
2/2013: MRCP(UK) Diploma. Member of the Royal collage of Physician, London, UK
6/2012: Passed the national Syrian first year medical exam with the Top-of-Nation ranking
8/2010: Medical Diploma (MD degree) (93.5%, Honor), Al Kalamoon University, Syria
6/2004: Baccalaureate degree 245/260 (94.4%, Honor)

Employment

01/2018-now: Cardiologist at University Heart Centre Lübeck, Germany
4/2017-now: Nucleus member of the Young Cardiology Section of the German Cardiac Society
4/2015-12/2017: Cardiology fellow at University Heart Centre Lübeck, Germany
5/2013 –3/2015: Cardiology fellow at Bayreuth Hospital, Bayreuth, Germany
1/2011-12/2012: Internal medicine resident in Damascus Hospital (Chef Resident), Syria

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Workshops and Courses

09/2017-03/2018: The European Physician Education Program **(E-PEP)** for device therapy
11/2014: Emergency physician training course, Sylt, Germany
6/2014: European Summer School of Internal medicine **(ESIM 2014)**, Sardinia, Italy

Languages

Arabic: native Language
English: Professional working proficiency**. IELTS (7 overall)**
German: Professional working proficiency. **C1 Level**

Memberships

- Member of the European Society of Cardiology (ESC)
- Member of the American Heart Association (AHA)
- Member of the European Preventive Cardiology Association (EAPC)
- Member of the Acute Cardiovascular Care Association (ACCA)
- Member (Gold) of the European Heart Failure Association (HFA)