The German–Austrian S3 Guideline “Cardiogenic Shock Due to Myocardial Infarction: Diagnosis, Monitoring, and Treatment”

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Abstract

Keywords
► cardiogenic shock
► myocardial infarction
► guideline
► percutaneous coronary intervention
► coronary artery bypass graft
► extracorporeal
► multiorgan dysfunction syndrome
► extracorporeal membrane oxygenation
► intra-aortic balloon counterpulsation
► ventricular assist device

Despite advances in the treatment of acute myocardial infarction with subsequent mortality reduction, which are mainly caused by the early timing of revascularization, cardiogenic shock still remains the leading cause of death with mortality rates still approaching 40 to 50%. Cardiogenic shock is characterized by a multiorgan dysfunction syndrome, often complicated by a systemic inflammatory response syndrome that affects the outcome more than the reduction of the cardiac contractile function. However, both European and American guidelines on myocardial infarction focus on interventional or surgical aspects only. Therefore, experts from eight German and Austrian specialty societies including the German Society for Thoracic and Cardiovascular Surgery published the German–Austrian S3 guideline “cardiogenic shock due to myocardial infarction: diagnosis, monitoring, and treatment” to provide evidence-based recommendations for the diagnosis and treatment of infarction-related cardiogenic shock in 2010 covering the topics of early revascularization, revascularization techniques, intensive care unit treatment including ventilation, transfusion regimens, adjunctive medical therapy, and mechanical support devices. Within the last 3 years, this guideline was updated as some major recommendations were outdated, or new evidence had been found. This review will therefore outline the management of patients with cardiogenic shock complicating acute myocardial infarction according to the updated guideline with a major focus on evidence-based recommendations which have been found relevant for cardiac surgery.
Introduction

Provided that they reach the hospital, patients with acute myocardial infarction (MI) have more than 90% probability of surviving. However, if cardiogenic shock occurs, either initially or in the course of infarction, only one in two survives. One main cause of the high mortality among patients with inhaled corticosteroids (ICS) is the development of multi-organ dysfunction syndrome (MODS) despite reperfusion of the infarcted vessel as early as possible. Consequently, ICS is not just a disease of the heart, but affects all organs of the patient, who therefore requires intensive care. The current European and American MI guidelines focus their recommendations mostly on “interventional aspects” in the treatment of the coronary artery disease; the “intensive care” aspect of the treatment of MODS, however, is insufficiently considered. This deficit prompted the German and Austrian cardiologists, intensivists, cardiac surgeons, anesthesiologists, and rehabilitation specialists, together with their professional societies and associations, to develop a S3 guideline for “infarction-related cardiogenic shock,” under the auspices of the Association of Scientific Medical Societies in Germany (AWMF, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften).

The aim of this German–Austrian guideline is to provide an adequate concept of both the cardiological/cardiosurgical and the intensive care aspects of ICS, since the prognosis of patients in this condition depends not only on the impaired cardiac function, but, even more, on the resulting impairment of organ blood supply and microcirculation with consequent MODS. Evidence on diagnosis, monitoring, and therapy of ICS was collected and recommendations compiled in a nominal group process by members of the German and Austrian Societies for Cardiology, Medical and General Intensive Care Medicine, Thoracic Cardiac and Vascular Surgery, Anaesthesiology and Intensive Care Medicine as well as Cardiovascular Preventive and Rehabilitation Medicine under the auspices of the German Guideline Working Group of Medical Scientific Societies (AWMF). A total of 95 recommendations—including two statements—and seven algorithms were assembled. The most relevant alterations/modifications as well as new recommendations in the updated guideline are given in Table 1. The full version and the guideline report are available at www.leitlinien.net (in German).

Medical Societies Involved in Guideline Development

Deutsche Gesellschaft für Kardiologie—Herz und Kreislauﬀorschung (DGK; German Cardiac Society; lead society) (K. Wedan as coordinator, M. Ruß as secretary with M. Kelm, H. Thiele, S. Willems, U. Zeymer, M. Ferrari, H. Figulla, G. Hindricks, P.M. Pieske, and J. Bauersachs).


Deutsche Interdisziplinäre Vereinigung für Intensivmedizin (DIVI; German Interdisciplinary Association of Intensive Care and Emergency Medicine) (A. Heller).

Österreichische Kardiologische Gesellschaft (ÖKG; Austrian Society of Cardiology) (G. Delle-Karth, E. Pichler-Cetin).

Deutsche Gesellschaft für Anästhesie und Intensivmedizin (DGAI; German Society of Anaesthesiology and Intensive Care Medicine) (B. Zwißler, J. Briegel).

Deutsche Gesellschaft für Prävention und Rehabilitation von Herzkreislauﬀerkrankungen (DGPR) (A. Schlitt).

Moderated by Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Gesellschaften (AWMF) (I. Kopp).

Contents of the German–Austrian S3 Guideline “Infarction-Related Cardiogenic Shock: Diagnosis, Monitoring, and Treatment”

- Introduction
- Method
- Synopsis: Diagnosis, monitoring, and treatment of infarction-related cardiogenic shock
- Definition, diagnosis, and monitoring
- Earliest possible coronary revascularization
- Cardiovascular support
- Treatment of complications of infarction-related cardiogenic shock
- Supportive therapy for multiorgan dysfunction syndrome (MODS)
- Nutrition and insulin therapy, red cell substitution and prophylaxis, considerations regarding limitation of treatment
- Aftercare and rehabilitation
- Recommendations “Gemeinsam Klug Entscheiden”
- Need for research

The Aims of the Guideline and Who the Guideline Is for

The aim of the S3 guideline “Infarktbedingter kardiogener Schock: Diagnose, Monitoring, und Therapie” (Infarction-Related Cardiogenic Shock: Diagnosis, Monitoring, and Treatment) is to improve the quality of care of patients with ICS, by publishing evidence-based recommendations. It also presents the “state of the art” in diagnostics, monitoring, and treatment, thus representing a starting point for comparative studies. This is particularly to be emphasized, because many of the recommendations in this S3 guideline are based on expert opinions due to the lack of high-quality evidence.

The recommendations in the S3 guideline are directed at physicians managing patients with shock and acute MI: that
is, in particular, cardiologists and specialists in internal medicine, intensivists, heart surgeons, anesthetists, physicians working in interdisciplinary emergency admission services, emergency physicians, and rehabilitation specialists, along with the care staff working with them.

Data Acquisition and Evaluation of Recommendations and Evidence

A systematic search of international guidelines was conducted to generate a statement of the thematic areas and questions on which there was consensus (‘source guidelines’; see Leitlinien report at www.leitlinien.net/). In addition, a primary systematic literature search was performed and publications from January 1, 1990 to September 30, 2009 (3,546 results) were included in the first version of this guideline. Publications from October 1, 2009 to January 31, 2019 were also included in this update. Evaluation of study quality and consecutive evidence as well as the assigning of recommendation grades was done using the nominal group process in accordance with the recommendation grades and evidence levels listed in Tables 2 and 3.

Diagnosis

Early Diagnosis of Cardiogenic Shock—It Is a Clinical Diagnosis

Cardiogenic shock after acute myocardial infarction (CS-AMI) develops within 6 hours in approximately 50% of the patients and within 24 hours in approximately 75% of the

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<th>Original guideline 2010</th>
<th>Updated guideline 2019</th>
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<td><strong>IABP</strong></td>
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<tr>
<td><strong>IABP with primary fibrinolysis:</strong></td>
<td>3/4† IABP with primary PCI: Routine use of IABPs in patients with cardiogenic shock due to MI is not recommended.</td>
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<tr>
<td>In patients with primary fibrinolysis, IABP should be performed adjuncively.</td>
<td>IABP with primary PCI: Routine use of IABPs in patients with cardiogenic shock due to MI is not recommended.</td>
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<td><strong>IABP with primary PCI:</strong></td>
<td>3/4--- IABP with CABG, fibrinolysis, or transfer: No recommendation can be made for patients undergoing revascularization with CABG or fibrinolysis and patients that have to be transferred.</td>
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<td>In patients with primary PCI, IABP may be considered, but the evidence is unclear.</td>
<td>EO</td>
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<td><strong>Patient transfer:</strong></td>
<td>3/4† Mechanical complications of MI: IABP may be used for hemodynamic stabilization in patients with mechanical complications of myocardial infarction including ventricular septal rupture, papillary muscle rupture.</td>
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<td>In patients that have to be transferred to an intervention center, IABP should be used.</td>
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**Temporary mechanical support system**

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<td>No recommendation</td>
<td>Short-term mechanical circulatory support can be considered in selected patients with MI and cardiogenic shock that cannot be quickly stabilized with conservative management.</td>
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**Culprit-lesion-only PCI vs. multivessel PCI**

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<td>In selected patients with coronary multivessel disease, complete revascularization during the index primary percutaneous coronary intervention (PCI) apart from the infarct-related artery (IRA) can be performed.</td>
<td>In patients with coronary multivessel disease and more than one significant stenosis, culprit-lesion-only-lesion preferred during the index PCI.</td>
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**Vascular access for PCI**

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<td>No recommendation</td>
<td>It is possible to use the transradial as well as the transfemoral access in patients with cardiogenic shock. It is recommended to choose the operators standard access in patients without acute coronary syndromes and cardiogenic shock.</td>
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**Post-infarction—ventricular septal defect**

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<td>Patients with a ventricular septal rupture should undergo urgent surgery after hemodynamic stabilization.</td>
<td>Patients with a ventricular septal rupture should undergo urgent surgery or percutaneous intervention.</td>
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<td>⇣ 3/4</td>
<td>⇣/ EO</td>
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Abbreviations: CABG, coronary artery bypass graft surgery; IABP, intra-aortic balloon counterpulsation; MI, myocardial infarction.
1. Systemic hypoperfusion
   (a) Oligo-/anuria <30 mL/h.
   (b) Cyanotic extremities.
   (c) Signs of cerebral hypoperfusion with somnolence and confusion.

Clinical Signs of Cardiogenic Shock

1. Blood pressure <90 mm Hg for more than 90 minutes.
2. Systemic hypotension.
3. Administration of catecholamines to stabilize the patient.
4. Use of intra-aortic counterpulsation.
5. Cardiac index <2.2 L/min/m².
6. Pulmonary capillary wedge pressure of >15 mm Hg.

Revascularization

Coronary reperfusion is the mainstay evidence-based therapeutic intervention for patients with acute MI presenting with CS. In this section, recommendations for reperfusion and revascularization techniques and other adjunctive therapies used in the management of CS are reviewed.

Timing

Early coronary revascularization is an essential therapeutic intervention for patients with ACS complicated by CS. However, the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial and the S(M)ASH (Swiss Multicenter Trial of Angioplasty for Shock, are the only randomized trials that examined the benefit of early revascularization in the setting of CS. Regrettably, the S(M)ASH was terminated prematurely due to insufficient patient enrollment.

The SHOCK trial demonstrated that, in patients with cardiogenic shock complicating AMI, emergency revascularization with PCI or coronary artery bypass graft (CABG) surgery improved long-term survival, compared with initial intensive medical therapy. All-cause mortality at 6 months was lower in the group assigned to revascularization than in the medically treated patients (50.3 vs. 63.1%, respectively; relative risk 0.80, 95% confidence interval 0.65–0.98, p = 0.03). A recent analysis of 12,675 STEMI patients in the FITT-STEMI (Feedback Intervention and Treatment Times in STEMI) trial emphasized the strong impact of time delays on mortality, particularly in STEMI patients with cardiogenic shock or out-of-hospital cardiac arrest. In shock without out-of-hospital cardiac
arrest, every 10-minute treatment delay between 60 to 180 minutes from the first medical contact resulted in 3.3 additional deaths per 100 PCI-treated patients and in 1.3 additional deaths after out-of-hospital cardiac arrest without cardiogenic shock.

Type of Revascularization
Coronary stenting is the technique of choice during primary PCI.\textsuperscript{14} Compared with balloon angioplasty alone, stenting with a bare-metal stent (BMS) is associated with a lower risk of reinfarction and target vessel revascularization. However, it is not associated with a reduction in the mortality rate. In primary PCI, drug-eluting stents reduce the risk of repeated target vessel revascularization compared with BMS. A sub-analysis of the SHOCK trial comparing patients treated with CABG or PCI showed similar survival rates between the two subgroups. There were more patients with diabetes (48.9 vs. 26.9%; \(p = 0.02\)), three-vessel disease (80.4 vs. 60.3%; \(p = 0.03\)), and LM coronary disease (41.3 vs. 13.0%; \(p = 0.001\)) in the CABG group. The results of this nonrandomized comparison suggest that CABG should be considered in patients with cardiogenic shock who have suitable anatomy, particularly if successful PCI is not feasible.

Recommendation 5.1.2.A. (Revascularization/PCI)
Emergency PCI of the culprit lesion is indicated for patients with cardiogenic shock due to STEMI or NSTE-ACS, independent of time delay of symptom onset, if coronary anatomy is amenable to PCI.

Recommendation 5.1.2.B. (PCI)
In patients presenting with ICS, prompt intervention with primary PCI within 90 minutes of first medical contact should be performed.
\*DGIIN: 90 minutes only for patients with cardiogenic shock due to a STEMI.

PCI Strategy
Culprit Lesion or Total Strategy
More than three-fourths of the patients in CS present with multivessel disease. Complete revascularization, addressing both culprit and hemodynamically significant non-culprit lesions, has historically been the preferred strategy in patients with acute MI and CS and was recommended in recent guidelines. However, this paradigm has recently been challenged. The CULPRIT-SHOCK (Culprit Lesion Only PCI vs. Multivessel PCI in Cardiogenic Shock) trial randomized 706 patients with STEMI/NSTEMI and an identifiable culprit lesion to multivessel or culprit lesion-only PCI.\textsuperscript{15} The composite primary end point was death or renal failure requiring dialysis at 30 days. The trial demonstrated a 9.5% absolute risk reduction of the composite primary end point in the culprit lesion-only group (7.3% of which was attributable to an absolute risk reduction in all-cause mortality). Of note, the culprit-lesion only cohort had the option for staged revascularization of nonculprit lesions and almost 20% of patients underwent further staged or urgent PCI. Additionally, 75 patients crossed over from culprit lesion-only to multivessel PCI raising the possibility of including more complex and comorbid patients in the multivessel PCI group, thus overestimating the benefit of culprit lesion-only PCI. Also, greater dye loads in multivessel PCI may partially account for observed differences observed. Another limitation of the study was that low rates of MCS device were used in the multivessel PCI group. One-year follow-up showed no mortality difference between the culprit lesion-only and multivessel PCI groups (50 vs. 56.9%, respectively). The CULPRIT-SHOCK trial contradicts widespread current practice and prior studies in nonshock patients (DANAMI-3-PRIMULTI, PRAMI, CvlPRIT) which suggested that there may be a benefit from complete revascularization.\textsuperscript{16–18}

Fibrinolysis
Fibrinolytic therapy is an important reperfusion strategy in settings where primary PCI cannot be offered in a timely manner and prevents 30 early deaths per 1,000 patients treated within 6 hours after symptom onset. The largest absolute benefit is seen among patients at highest risk, including the elderly, and when treatment is offered <2 hours after symptom onset.\textsuperscript{19} Fibrinolytic therapy is recommended if primary PCI cannot be performed within 6 hours from MI diagnosis and there are no contraindications. If the patient is presented later (particularly after 3 hours), more consideration should be given to transfer for primary PCI (as opposed to administering fibrinolytic therapy) because the efficiency and clinical benefit of fibrinolysis decrease as the time from symptom onset increases. In the presence of contraindications for fibrinolytic treatment, it is important to weigh the potentially life-saving effect of fibrinolysis against potentially life-threatening side effects, taking into account alternative treatment options such as delayed primary PCI.

Recommendation 5.2.4.A (Culprit lesion PCI) In patients with coronary multivessel disease and more than one significant stenosis, culprit-lesion-only-lesion during the index PCI is preferred.

Fibrinolytic therapy should be performed in patients with ICS if early coronary angiography and revascularization cannot be performed within 6 hours. Coronary angiography should be performed as soon as possible.

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Surgical Revascularization (Coronary Artery Bypass Graft Surgery)
Emergent CABG surgery should be considered for patients with cardiogenic shock with a patent IRA but with unsuitable anatomy for PCI. In patients with MI-related mechanical complications who require coronary revascularization, CABG is recommended at the time of repair. In MI patients with failed PCI or coronary occlusion not amenable to PCI, emergent CABG is infrequently performed because the benefits of surgical revascularization in this setting are uncertain. As the delay to reperfusion is long, the probabilities of myocardial salvage affecting prognosis are low and the surgical risks are elevated.

In a propensity-matched comparison from the ACUITY trial, moderate- and high-risk patients with ACS and multivessel disease treated with PCI rather than CABG had lower rates of periprocedural stroke, MI, major bleeding, and renal injury, with comparable 1-month and 1-year rates of mortality, but more frequently developed recurrent ischemia requiring repeated revascularization procedures during follow-up. However, recently published studies indicate a reasonable survival rate in patients with acute MI complicated by cardiogenic shock. Therefore, early CABG should be performed in patients with a coronary anatomy not suitable for PCI and should be discussed as alternative to PCI in patients with complex coronary anatomy after interdisciplinary evaluation of the Heart Team.

**Recommendation 5.2.5.A. (Complex coronary anatomy or failed percutaneous PCI)**
In patients with complex coronary anatomy emergency surgical or interventional revascularization should be performed as decided by the interdisciplinary Heart Team. Emergency CABG is recommended for patients with cardiogenic shock if the coronary anatomy is not amenable to PCI.

**Recommendation 5.3.3.B (Complex coronary anatomy or pathology and mechanical complication of myocardial infarction)**
In patients with complex coronary anatomy and mechanical complications of MI, emergency surgical or interventional therapy is indicated, as decided by the interdisciplinary Heart Team.

Mechanical Circulatory Support
Escalating doses of vasopressors and inotropes are associated with significant limitations including arrhythmias, increased myocardial oxygen consumption, and inadequate circulatory support as well as increased mortality. Therefore, mechanical circulatory support is an essential part of the management of cardiogenic shock and is commonly utilized as a bridge-to-decision, whether it is recovery, palliation, heart transplantation, or a durable mechanical circulatory support device. Options for acute percutaneous MCS include the intra-aortic balloon pump (IABP), axial flow pumps (Impella LP 2.5, Impella CP), left atrial-to-femoral arterial ventricular assist devices (Tandem Heart), and venous-arterial extracorporeal life support (ECLS).

**IABP**
Since its introduction into clinical practice >50 years ago, intra-aortic balloon counterpulsation has been used empirically to provide hemodynamic support in patients undergoing coronary revascularization in the setting of MI and cardiogenic shock. In the landmark SHOCK trial, conducted between 1993 and 1998, IABPs were implanted in 86% of the participants, irrespective of the assigned management strategy. However, despite its widespread use and high recommendations in international guidelines, the last version of the German–Austrian S3 guideline gave only a weak recommendation for the use of IABP in ICS patients treated with systemic fibrinolysis, and only "may" information for patients treated with PCI as there were no randomized controlled trials showing a benefit of aortic counterpulsation.

The IABP-SHOCK II (Intra-aortic Balloon Pump in Cardiogenic Shock II) trial randomly assigned 600 participants planned for early revascularization of acute MI complicated by cardiogenic shock to either IABP placement or no IABP placement. The primary end point was 30-day all-cause mortality. After 30 days or at day 30, all-cause mortality was 40%, with no difference between patients randomized to receive an IABP versus those who were not. There were no differences between treatment groups in secondary outcomes, including bleeding, ischemic complications, stroke, time to hemodynamic stabilization, intensive care unit length of stay, and the dose and duration of catecholamine therapy. At 6 years of follow-up, all-cause mortality was high and did not differ between the IABP and control groups (62.5% vs. 67.0%) in intention-to-treat, per-protocol, and as-treated analyses. No signal for benefit associated with IABP use was observed in any prespecified or post hoc subgroups. There were no differences in the frequency of recurrent MI, repeat revascularization, stroke, or cardiovascular rehospitalization between the two groups. Quality of life, measured by the EuroQol 5D questionnaire and New York Heart Association classification, was favorable in survivors of cardiogenic shock. Four of five survivors had New York Heart Association Class I or II symptoms, with no difference between patients randomly assigned to IABP and no IABP therapy. Based on the current evidence, IABP placement cannot be recommended routinely in patients with ICS.

**Recommendation 7.3.7.A. (IABP in patients with PCI)**
Routine use of IABPs in patients with cardiogenic shock due to ACS is not recommended.

**Recommendation 7.3.8.A. (IABP in patients with mechanical**
Other Mechanical Circulatory Support Systems

Alternative percutaneous left ventricular assist devices (LVADs)—centrifugal pumps without oxygenator (Tandem Heart) and with oxygenator (venoarterial extracorporeal membrane oxygenation, LifeBridge) as well as axial flow pumps (Impella Recover LP2.5 and Impella Recover LP5.0) are hemodynamically more effective than the IABP. The choice of which MCS device to be used is based on many factors, including type of shock (right heart failure, left heart failure) as well as operator abilities and institutional resources.

A recent meta-analysis on MCS in cardiogenic shock included four randomized trials investigating the efficacy and safety of percutaneous LVADs versus IABP, and demonstrated similar short-term mortality despite initial beneficial effects on arterial blood pressure and peripheral perfusion, measured by serum lactate levels. In all trials, a higher rate of bleeding from vascular access sites and a significantly higher incidence of limb ischemia following percutaneous LVAD was notable. In summary, the evidence for mechanical circulatory systems is insufficient to provide a recommendation on its routine clinical use in cardiogenic shock.

A recently published meta-analysis comparing mortality in patients treated with and without ECLS support included 13 studies in which nine studies dealt with cardiac arrest patients (n = 3098) and four studies with patients suffering from cardiogenic shock after acute MI (n = 235).

In cardiac arrest, the use of ECLS was associated with an absolute increase of 30 days survival of 13% compared with patients in which ECLS was not used and a higher rate of favorable neurological outcome was achieved at 30 days. In cardiogenic shock, ECLS showed a 33% higher 30-day survival compared with IABP but no difference when compared with TandemHeart/Impella.

Therefore, the current guideline suggests that short-term mechanical circulatory support can be considered in selected patients with ACS and cardiogenic shock that cannot be rapidly stabilized with conservative management if:

- MCS implantation does not delay emergency revascularization.
- There is a clear patient-specific therapeutic goal as evaluated and documented by the Heart Team.
- There is a structured cooperation with a heart-failure center for early destination therapy.
- Patients are enrolled in a registry for MCS of the participating medical societies.

The choice of which MCS device to be used is based on many factors, including type of shock (right heart failure, left heart failure) as well as operator abilities and institutional resources.

**Mechanical Complications of MI**

**Ventricular Septal Rupture**

Ventricular septal rupture may occur within 24 hours to several days after MI and usually presents as rapid-onset clinical deterioration with acute heart failure or cardiogenic shock. The diagnosis is confirmed by echocardiography. IABP may stabilize patients in preparation for angiography and surgery.

Surgical repair may be required urgently, but there is no consensus on the optimal timing for surgery. Early surgery is associated with a high mortality rate, reported as 20 to 40%, and a high risk of recurrent ventricular rupture, while delayed surgery allows easier septal repair in scarred tissue but carries the risk of rupture extension and death while waiting for surgery. Therefore, early surgery should be performed in all patients with severe heart failure that does not respond rapidly to aggressive therapy, but delayed elective surgical repair may be considered in patients who respond well to aggressive heart failure therapy. Percutaneous closure of the defect with appropriately designed devices may soon become an alternative to surgery.

**Recommendation 8.4.2.A.**

* (Ventricular septal rupture) Patients with a ventricular septal rupture should undergo urgent surgery or percutaneous intervention.

**Papillary Muscle Rupture**

Acute mitral regurgitation may occur 2 to 7 days after AMI due to rupture of the papillary muscle or chordae tendineae. The rupture may be complete or involve one or more of the heads and is 6 to 12 times more frequent in the postero-medial papillary muscle because of its single artery blood supply. Papillary muscle rupture usually presents as sudden hemodynamic deterioration with acute dyspnea, pulmonary edema, and/or cardiogenic shock. Immediate treatment is based on afterload reduction to reduce regurgitant volume and pulmonary congestion. Intravenous diuretic and vasodilator/inotropic support, as well as IABP, may stabilize patients in preparation for angiography and
surgery. Emergency surgery is the treatment of choice although it carries a high operative mortality (20–25%).

### Recommendation 8.4.4.A.
(Acute severe mitral regurgitation)
Patients with a significant acute mitral regurgitation should undergo urgent surgery.

**Author’s Contribution**
All authors participated sufficiently in the work to take public responsibility for the content. K.W. and M.R. designed the research/study and analyzed data. K.P., K.W., M.R., H.T., G.M., U.B., and M.T. performed study research. K.P., U.B., M.T. wrote the paper. U.B., H.T., and K.W. did the supervision and all the authors did the critical revision of the manuscript.

**Conflict of Interest**
None.

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