ST-Elevation Myocardial Infarction (STEMI) In Elderly with Biomarkers Roles In Contrast Induced Nephropathy

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Abstract

Background: Contrast-induced nephropathy (CIN) is associated with an increased risk of major adverse cardiovascular events (MACE), and the association between CIN and oxidative mechanisms is well documented. Several novel renal biomarkers have been proposed to predict early CIN, like kidney injury marker 1 (KIM-1) and cyt C. KIM-1 is a type-1 transmembrane protein, expressed according to the injury in the proximal tubule of the apical membrane. Many studies show that KIM-1 is a sensitive and specific marker of kidney injury as well as a predictor of prognosis especially in acute kidney injury

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Introduction:

ST-Segment elevation myocardial infarction, usually occurs when a fibrin-rich clot completely blocks an epicardial coronary artery, and accounts for about 25-40% cases of acute coronary syndrome (ACS) ***(1).***

ST-segment elevation myocardial infarction (STEMI) requires timely reperfusion therapy, which may be carried out by two treatment strategies: primary percutaneous coronary intervention (PPCI) or a pharmacoinvasive strategy (PIs). A lower mortality rate has been reported in patients who receive PPCI in clinical trials conducted in high-volume centers and with adequate ischemic times. The choice of reperfusion strategy depends on several factors. In the case of PPCI, adequate hospital infrastructure along with suitable equipment and logistics are required, in addition to trained human resources **(2).**

Another relevant factor to be considered is the delay in time until the selected strategy is applied. It is recommended that reperfusion be performed within the first 12 h after symptom onset, since

the earlier the therapy is applied the higher the survival rate. However, in a large percentage of patients, PPCI is not achieved within the recommended time and is associated with an increase in morbidity and mortality. This increase in morbidity and mortality has been described in international registries, reporting worse outcomes in the 5-year follow-up of patients undergoing late PPCI compared to patients undergoing PIs (*3*).

In low-to-middle-income countries, the proportion of patients with STEMI who receive a prompt PPCI reperfusion is low. Therefore, the greater availability and relative simplicity associated with the administration of a fibrinolytic agent with the pharmaco-invasive makes this approach a reasonable alternative when prompt PPCI (within the first 120 min of diagnosis) cannot be administered (2).

Clinical practice guidelines recommend that patients who are diagnosed with STEMI prior to hospital admission be delivered directly to a primary PCI center in order to minimize treatment times. However, many patients with STEMI either self-present to hospitals which do not provide PCI or are taken there by paramedics because a prehospital diagnosis of STEMI is not made. Between 2012 and 2016 approximately 20% of STEMI patients in the UK were initially assessed at a non-PCI performing hospital and then subsequently transferred to a primary PCI performing center. This transfer to a PCI center can potentially result in long delays to reperfusion in comparison with patients who are admitted directly to a PCI center (4).

Cardiovascular disease (CVD) is the main cause of death and disability worldwide. Acute myocardial infarction is a myocardial necrosis due to prolonged ischemia. The diagnosis is based on biochemical criteria (troponin elevation as a result of irreversible cell damage), clinical evaluation, ECG findings, invasive and noninvasive imaging and pathological evaluation *(4).*

It is estimated that globally, IHD affects around 126 million individuals (1,655 per 100,000), which is approximately 1.72% of the world's population. Nine million deaths were caused by IHD globally. Men were more commonly affected than women, and incidence typically started in the fourth decade and increased with age *(5).*

Considerable variance in outcomes may depend importantly upon patients' age, race and gender, as well as the treatment facility itself. Being black, female or of advanced age confers relatively higher mortality in the US, while STEMI mortality is consistently lower in hospitals that manage higher patient volumes and have busier procedural centers *(6).*

It is widely accepted that the majority of ACS events are caused by an episode of acute thrombosis in the presence of coronary atherosclerotic disease. Episodes of angina or myocardial infarction can occur in the absence of coronary atherosclerosis, but, in these particular cases, both treatment and prognosis are different from those present when ACS is associated with underlying atherosclerotic changes (7).

. Non atherosclerotic causes of myocardial infarction include the following:

- Coronary occlusion secondary to vasculitis

- Ventricular hypertrophy (e.g , left ventricular hypertrophy, idiopathic hypertrophic subaortic stenosis, underlying valve disease)

- Coronary artery emboli, secondary to cholesterol, air, or the products of sepsis
- Congenital coronary anomalies
- Coronary trauma
- Primary coronary vasospasm (variant angina)
- Drug use (e.g , cocaine, amphetamines, ephedrine)
- Factors that increase oxygen requirement, such as heavy exertion, fever, or hyperthyroidism
- Factors that decrease oxygen delivery, such as hypoxemia of severe anemia
- Infected cardiac valve through a patent foramen ovale **(8).**

In addition, myocardial infarction can result from hypoxia due to carbon monoxide poisoning or acute pulmonary disorders. Infarcts due to pulmonary disease usually occur when demand of the myocardium dramatically increases relative to the available blood supply **(*9*).**

III. Diagnosis

According to the fourth universal definition of myocardial infarction, the term **acute myocardial infarction (AMI)** should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI:

1. **Detection of a rise and/or fall of cardiac biomarker values** [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following: **(*10*).**

- Symptoms of ischemia.
- New or presumed new significant ST-segment–Twave (ST–T) changes or new left bundle branch block (LBBB).
- Development of pathological Q waves in the ECG.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Identification of an intracoronary thrombus by angiography or autopsy.

2. **Cardiac death with symptoms suggestive of myocardial ischemia** and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.

3. **Percutaneous coronary intervention (PCI) related MI** is arbitrarily defined by elevation of cTn values (>5x 99th percentile URL) in patients with normal baseline values (99th percentile URL)or arise of cTn values > 20% if the baseline values are elevated and are stable or falling .In addition, either **(I)** symptoms suggestive of myocardial ischemia or **(II)** new ischemic ECG changes

or **(III)** angiographic findings consistent with a procedural complication or **(IV)** imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

4. **Stent thrombosis associated with MI** when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with arise and /or fall of cardiac biomarker values with at least one value above the 99th percentile URL.

5. **Coronary artery bypass grafting (CABG) related MI** is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (99th percentile URL). In addition, either **(I)** new pathological Q waves or new LBBB, or **(II)** angiographic documented new graft or new native coronary artery occlusion, or **(III)** imaging evidence of new loss of viable myocardium or new regional wall motion abnormality **(*10*).**

Two-dimensional echocardiography is of particular value when the diagnosis of STEMI is uncertain, and other causes of chest pain such as acute aortic dissection, pericardial effusion, or pulmonary embolism are being considered. The performance of echocardiography should not delay the initiation of treatment ***(11).***

IV. Treatment

Thrombolytic drugs and primary PCI are the two reperfusion strategies currently available to open the infarct-related artery. Achieving an early and complete restoration of blood flow, with resultant improvement in myocardial perfusion, is the main goal in the management of STEMI patients **(7).**

Cardiovascular disease poses a growing burden as age increases, and it remains the leading cause of morbidity and mortality in the elderly. Indeed, age is the strongest risk factor for the development of coronary heart disease **(12).**

MI occurs once every 40 seconds in the U.S., with an estimated annual incidence of 605,000 new cases and 200,000 recurrent cases .The average age of incidence of a first MI is 65.1 for men and 72 for women. MI mortality in the U.S. was 27.0 per 100,000 in 2018. Approximately 38% of patients who present to the hospital with acute coronary syndrome have an ST-elevation myocardial infarction ***(13).***

Cardiovascular disease has been the leading cause of death worldwide. With the acceleration of population aging, the number of elderly patients with acute ST-segment elevation myocardial infarction (STEMI) is also increasing, posing a considerable challenge to social health care Percutaneous coronary intervention (PCI) is currently the mainstay of treatment for patients with acute STEMI, but contrast-induced acute kidney injury (CI-AKI) occurs in 15–35% of patients after PCI **(13).**

Compared to younger patients, the elderly present with more comorbidities and are at higher risk of mortality and complications following percutaneous coronary intervention (PCI) especially those with acute coronary syndromes or ST-elevation myocardial infarction (STEMI) **(14).**

Elderly patients are more likely to present with atypical symptoms, increasing the risk of delay in treatment or misdiagnosis. In the setting of ST-segment elevation myocardial infarction (STEMI),

older patients were the principal population to benefit from the introduction of primary PCI (pPCI) due to the high rates of major bleeding, particularly intracranial bleeding, associated with fibrinolysis therapy **(15)**.

Even in very old patients, the performance of pPCI has been shown to be both feasible and effective.Hence, age should not be an exclusion criterion for undergoing pPCI in older patients with STEMI, as recommended by the latest clinical guidelines. Both the European and American guidelines emphasize that there is no upper age limit for reperfusion, and in the elderly population, as in younger patients, an early invasive strategy is preferred **(16)**.

Impact and Role of Geriatric Conditions and Comorbidity

1. Frailty

Frailty is considered as a marker of the individual's biological age and constitutes a decrease in the physiological reserve, representing a state of vulnerability with a higher risk of adverse events **(17)**.

It is prevalent in older patients with acute and chronic cardiovascular disease, entailing a worse prognosis in both the long and the short term **(18)**.

In ACS settings, frail patients less frequently undergo an invasive strategy, and they often receive lower prescriptions of potent antiplatelet therapies and secondary prevention drugs.This may be due to a higher concern about side effects, including higher perceived morbidity and mortality **(19)**.

2. Sarcopenia

Sarcopenia is an age-related syndrome characterized by a loss of muscle mass that also involves a decrease in muscle strength and/or physical capacity.The prevalence of sarcopenia is 5–15% in patients > 65 years, but it can be higher in hospitalized older adults with coronary heart disease (22.6–43%). Sarcopenia increases the risk of falls and fractures, impairs the ability to perform activities of daily living (ADLs), and contributes to lowered quality of life (QoL), higher institutionalization, and death.On the other hand, the presence of sarcopenia is also associated with cardiorespiratory diseases and adversely affects the cardiovascular system, causing endothelial and vascular dysfunction **(20)**.

However, sarcopenia is a preventable and reversible geriatric syndrome, as it can be treated. For this purpose, it is essential to consider the interrelationship with other syndromes such as cachexia, malnutrition, and frailty, requiring a comprehensive geriatric assessment **(15)**.

The two main pillars for managing sarcopenia are nutrition and physical exercise. Regarding nutrition, a high-protein diet (1–1.2 g of protein/kg/day) is recommended since the requirements for older adults are higher than those for young individuals to maintain muscle mass. Furthermore, intakes should be balanced (high volumes slow gastric emptying and induce satiety), with around 15–20 g of protein recommended at each meal. It is also important to avoid fasting, and although the superiority of animal protein over plant-based protein has not been proven, the best muscle synthesis performance is achieved with protein intake after physical exercise. Other supplements such as creatine or beta-hydroxy-beta-methylbutyrate are showing promising results in this regard **(21)**.

3. Cognitive Impairment and Delirium

Cognitive impairment is defined as a disruption to some cognitive function such as memory. According to the Diagnostic and Statistical Manual of Mental Disorders DSM-5 criteria, a major neurocognitive disorder, which corresponds to dementia, requires substantial impairment to be present in one or, usually, more cognitive domains **(22).**

There is a relationship between cognitive impairment and MI. **Johansen et al.** found that incident MI was not associated with a decrease in global cognition at the time of the event but was associated with faster declines in global cognition, memory, and executive function over time **(23).**

Therefore, post-acute MI is a risk factor for developing cognitive impairment, and preventing MI is important to preserve brain health. On the other hand, delirium is a neuropsychiatric characterized by an acute change in attention and other aspects of cognition such as altered arousal, disorientation, psychosis, or mood disturbance. The incidence of delirium in Intensive Care Unit (ICU) after acute MI is around 30%, and it is associated with several poor outcomes such as a longer hospital stay, functional decline, falls, incident dementia, and higher in-hospital death **(24).**

Delirium prevention is also possible, being the best option to avoid its terrible consequences. The **ABCDEF** bundle component was developed in ICU for this purpose:

- **A**ssess and treat pain.
- **B**reathing trials to avoid over-sedation.
- **C**hoice of sedation avoiding benzodiazepines to perform a light sedation.
- Identify and manage **D**elirium risk factors such as a disordered sleep–wake cycle or vision/hearing impairment.
- **E**arly mobility.
- **F**amily engagement to avoid nocturnal disorientation **(25).**

4. Comorbidity

Comorbidity is defined as the co-occurrence of several diseases. In the elderly population with ACS, comorbidity is common and significantly impacts prognosis.Current guidelines recommend its routine assessment. Preceding studies suggest that, as the burden of comorbidity increases, the likelihood of undergoing invasive treatment decreases. However, it is important to note that, as comorbidity increases, so do the ischemic and hemorrhagic risks **(26).**

CKD affects up to 75% of older adults with an ACS, conferring a worse prognosis with higher mortality and readmission rates. In fact, CKD stands out as one of the main causes of non-referral to revascularization procedures in ACS patients. Nevertheless, a comprehensive meta-analysis involving over 3000 patients revealed that revascularization, in comparison to medical therapy, entailed a lower incidence of MI in individuals with CKD. Anemia is found in 15–20% of ACS patients, but its prevalence increases in up to 43% in the elderly subgroup of patients with ACS. Anemia is a powerful predictor of mortality in ACS after adjustment for most clinical variables and frailty **(27).**

Malignancy represents the second most common cause of death globally and it becomes more prevalent with age.Cancer and cardiovascular conditions are commonly associated as they share risk factors. This association can also be influenced by the state of chronic inflammation that is present in both neoplastic diseases and frailty **(17)**. Furthermore, the oncological therapies themselves may enhance the atherosclerotic process, endothelial dysfunction, thrombosis, and coronary spasm, both in active cancer patients and years after recovery **(28)**.

Cardiovascular diseases have a significant impact on the elderly, but effective implementation of secondary prevention faces challenges due to their vulnerable characteristics and the limited scientific data. Managing traditional cardiovascular risk factors is crucial for older individuals following cardiovascular events **(15)**.

Table (1): Recommendations about control of traditional cardiovascular risk factors in the elderly (15).

Risk Factor	**Recommendations**
Hypertension	Target blood pressure < 140/80 mmHg, even <130 mmHg if tolerated. Lenient control if frailty or very older (>80 years)
Diabetes	Target glycated hemoglobin level of 7–7.5%. Lenient control in frail or terminal ill patients, avoiding hypoglycemia.
Dyslipidemia	Target LDL-cholesterol ≤ 55 mg/dL and >50% baseline reduction in very high cardiovascular risk patients.
Smoke	Smoke cessation
Diet	Adherence to Mediterranean diet.
Obesity	Overweight may be permitted. Avoid obesity.

Kidney injury molecule 1 (KIM-1) In Contrast Induced Nephropathy

Several novel renal biomarkers have been proposed to predict early CIN, like kidney injury marker 1 (KIM-1) and cyt c. KIM-1 is a type-1 transmembrane protein, expressed according to the injury in the proximal tubule of the apical membrane. Many studies show that KIM-1 is a sensitive and specific marker of kidney injury as well as a predictor of prognosis especially in acute kidney injury **(29)**.

KIM-1 mediates epithelial phagocytosis in the injured kidney converting the proximal epithelial cell into a phagocyte, with potentially important pathophysiological implications for modulation of the immune response and repair process after injury. Kidney injury molecule 1

(KIM-1), also known as T-cell immunoglobulin mucin 1 (TIM-1), is a transmembrane glycoprotein mostly expressed by renal proximal tubular cells (**30).**

The extracellular domain of KIM-1 is cleaved by matrix metalloproteinases and is present in the urine of rodents and humans after proximal tubular injury. It has been recognized as an early, sensitive and specific urinary biomarker for kidney injury, in both rodent models and in humans **(31).**

In an acute setting, KIM-1 has anti-inflammatory and protective properties as it can transform epithelial cells into semiprofessional phagocytes by linking phosphatidylserine on dead cells **(30).**

However, chronic overexpression in tubular cells can lead to inflammation and interstitial fibrosis **(31).**

More recently, elevated circulating levels of KIM-1 in blood were associated with acute and chronic kidney damage **(30).**

Kidney injury molecule 1 is a promising marker for early detection of AKI, and its concentration is markedly increased within hours following kidney injury. It is a type I transmembrane glycoprotein with two extracellular domains. After injury, the extracellular domains of KIM-1 separate from the cell surface and enter the urine. KIM-1 expression is low in normal kidneys but is significantly increased in proximal tubule cells following AKI **(32).**

Cytochrome c (cyt c) In Contrast Induced Nephropathy

Cytochrome c is a small, water-soluble protein of molecular weight about 12,000. It is a peripheral membrane protein since it can be readily stripped (without detergent) from mitochondrial membranes where it is found. Cytochrome c is associated with specific binding sites on integral membrane proteins extending from the membrane surface. Cytochrome c is approximately spherical in shape. The topology for the amino acids of this protein is typical of that normally found for water-soluble proteins. Polar amino acid residues largely reside on the outer surface of the protein, whereas hydrophobic amino acids are largely located in the interior of the protein. The hydrophobic effect is satisfied by this topology. As a result, cytochrome c is readily soluble in aqueous phase **(33).**

Cytochrome c is a key protein that initiates the intrinsic apoptosis pathway. Interestingly, cytochrome c itself undergoes antiapoptotic modification by glucose metabolism . The pentose phosphate pathway generates NADPH, which controls redox state of cells through production of glutathione. It was showed that NADPH derived from the pentose phosphate pathway controls redox state of cytochrome c. In the reduced form, cytochrome c is not capable of inducing efficient apoptosome formation. Conversely, in the oxidized form, which can be created by ROS, cytochrome c can readily trigger apoptosome assembly. These results indicate that glucose metabolism negatively regulates apoptosis even downstream of MOMP through the production of NADPH. In this regard, it is noteworthy that nucleotides can directly bind to cytochrome c and prevents its interaction with APAF-1. Thus, it is possible that NADPH derived from the pentose phosphate pathway also directly contributes to the metabolic inhibition of cytochrome c. **(33).**

Cytochrome c (cyt c) is a hemoprotein that normally attaches to the outer surface of the inner mitochondrial membrane in a form that binds to cardiolipin and plays an important physiological role in oxidative phosphorylation (**34).**

There were studies shown that elevated levels of circulating cyt c were closely associated with myocardial infarction, acute kidney injury, and systemic inflammatory response syndrome. several novel renal biomarkers have been proposed to predict early CIN, including Antithrombin III, neutrophil gelatinase-associated lipocalin (NGAL), cyt c, and kidney injury marker 1 (KIM-1). The cyt c is released from the mitochondrial membrane to the cytoplasm, which activates caspase 3 and eventually leads to apoptosis **(35).**

The cyt c is a key factor in initiating mitochondrion-mediated apoptosis pathway and is closely related to cell apoptosis. The cyt c is located in the surface of inner mitochondrial membrane and plays a key role in mitochondrial energy metabolism. It can be released from mitochondria to cytosol when cells undergo apoptosis under various factors. There were studies which had shown that circulating cyt c levels are associated with electrocardiographic and angiographic signs of impaired myocardial reperfusion, extension of infarct size, and 1-year mortality. Mitochondrial dysfunction causes a decrease in ATP production, alterations in cellular structure and functions, and the reduction of renal function. ROS can trigger cell apoptosis by causing the release of cytochrome c, leading to mitochondrial dysfunction **(36).**

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