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In-hospital cardiac mortality: Epidemiology and prevention strategies

Mortalidad cardíaca intrahospitalaria: Epidemiología y estrategias de prevención

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ABSTRACT

Mortality from cardiac causes has been extensively evaluated in the outpatient context; however, studies related to this topic in hospitalized patients are scarce. The literature review showed that non atherosclerotic ischemic diseases and acute pulmonary embolism are more frequent in recently operated patients; while in those admitted for medical reasons, the acute pulmonary embolism, acute heart failure and cardiorespiratory arrest can be present. In patients admitted to the acute care units predominated the non-atherosclerotic ischemic events, mainly related to states of shock, cardiorespiratory arrest, acute pulmonary embolism and acute heart failure. The evaluation and control of cardiovascular risk factors, maintenance of basic treatment, correction of acute pathophysiological changes, mobilization and early rehabilitation, thromboprophylaxis and protocoled care, are the main prevention strategies to be followed. Adequate clinical trials are required to verify the efficacy and safety of prophylactic measures.

RESUMEN

La mortalidad de causa cardíaca se ha evaluado extensamente en el contexto extrahospitalario; sin embargo, los estudios relacionados con este tema en los pacientes hospitalizados son escasos. La revisión de la literatura indica que en los pacientes recién operados son más frecuentes las enfermedades isquémicas no ateroscleróticas y el embolismo pulmonar agudo; y en los ingresados por causas médicas, el embolismo pulmonar agudo, la insuficiencia cardíaca aguda y el paro cardiorrespiratorio. En los enfermos ingresados en unidades de atención al paciente grave predominan los episodios isquémicos no ateroscleróticos, principalmente relacionados con estados de shock, el paro cardiorrespiratorio, el embolismo pulmonar agudo y la insuficiencia cardíaca aguda. La evaluación y control de los factores de riesgo cardiovascular, el mantenimiento del tratamiento de base, la corrección de las alteraciones fisiopatológicas agudas, la movilización y rehabilitación precoz, la tromboprofilaxis y la atención protocolizada, son las principales estrategias de prevención. Se necesitan ensayos clínicos adecuados para comprobar la eficacia y seguridad de las medidas profilácticas.

INTRODUCTION

In the hospital context, it is often necessary to distinguish between the patient who develops a cardiores-

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piratory arrest (CRA) and the patient who dies as a result of the evolutionary course of his/her disease. This distinction is important, because death involves a cessation of cardiac and respiratory functions, similar to what happens in the CRA.

According to the international guidelines[1], death is defined as "... the permanent loss of consciousness and all functions of the brainstem. It may result from a permanent cessation of circulation or a catastrophic brain damage (...) permanent refers to the loss of function that cannot be restored spontaneously and may not be restored by any intervention"[1]. Therefore, although in the CRA there is a cessation of circulation, this situation is not assumed to be permanent, and it is resettable by spontaneous circulation through cardiopulmonary resuscitation[2].

When death is studied, it is necessary to research about its causes, which may or may not be related to heart diseases. Death for a cardiac cause, or simply cardiac death, means: a) that one directly caused by a cardiac complication, b) death with not defined cause c) when the identified cause cannot lead to death itself, especially in a patient who was not expected to die[3-5].

Cardiac death may occur in the out-of-hospital or in-hospital environments. In the second one, the patient may have acquired the cause that originated it before admission, which is usually the "source of admission", or during the stay at the hospital. The latter option is what is discussed in this article, because it is usually a result of health care and it might be conceptually preventable[6]; besides having important implications from the epidemiological and management point of view.

Cardiac death, in the context of cardiac surgery or peri-interventional procedure, was not included in this review, because these are particular scenarios widely studied and shown in the literature. The purpose of this study is to examine the epidemiological characteristics of in-hospital cardiac death, its main causes and prevention strategies.

METHOD

A literature review was conducted during September and October 2016. Epidemiological studies, clinical trials, systematic reviews and literature reviews that exposed the incidence/prevalence of major causes of in-hospital cardiac death were reviewed, as well as prevention strategies.

Databases as MEDLINE, EMBASE, Cochrane Library (included Cochrane Database of Systematic Reviews and Cochrane Controlled Trials Register), CINAHL and SciELO were consulted for these purposes. All databases were searched using the following keywords: "cardiac death", "hospital mortality", "pulmonary embolism", "myocardial acute infarction", "acute heart failure" and "in-hospital cardiac arrest".

Bibliographic citations of the selected studies were reviewed to find other potentially eligible studies. Only articles in Spanish and English were reviewed. There were selected, preferably, articles published from 2000, in order to judge the evidence in the present context.

RESULTS

Hospitalized patients are at risk of developing cardiac complications. Many pathophysiological changes such as hypoxemia, hypotension, renal dysfunction, neurological disorders and anemia have a direct or indirect effect on the cardiovascular system. Cardiac and non-cardiac therapeutic interventions or procedures as drugs, coronary catheterization and surgery (cardiac or not) can also affect the heart[6].

At the in-hospital environment, patients can be divided into three groups according to the type of treatment they receive: surgical, medical and critic. This distinction is important because the risk of developing complications involving cardiac death is –partly– influenced by the group to which each patient belongs. Surgical patients are at increased risk of acute myocardial infarction (AMI) and acute pulmonary embolism (APE), while medical patients often develop APE, acute heart failure (AHF) and CRA; meanwhile, critically ill patients are at risk of developing any cardiac complications.

In a recent study of patients undergoing surgery for chest and gastrointestinal cancer, our group found that 11.7% developed postoperative cardiovascular complications[7]. Such complications are independently associated with hospital mortality in the multivariate analysis (odds ratio [OR], 5.06; 95% CI 1.49-17.13; p=0.009)[7], which demonstrates the need for active research and systematic implementation of prevention strategies. In another study, by Martos and Gutiérrez[8], it was found that 8.2% of patients operated for cancer of any location developed some cardiovascular complication. In this study was iden-

tified that the cardiac risk index greater than or equal to two points, gastrointestinal surgery and thoracic surgery were associated with an increased risk of complications of this type; moreover, the presence of at least one cardiovascular complication, critical cardiovascular complications, the CRA and the AHF were independent risk factors of hospital death[8]. Therefore, special attention must be paid to preoperative measures for risk stratification and timely action against modifiable factors, besides keeping a close eye during and after surgery.

Acute pulmonary embolism

Despite major medical advances in recent years, the APE continued to be a cardiovascular emergency associated with high morbidity and mortality. At its clinical suspicion, prompt treatment aimed at correcting the pathophysiological changes and prevent the occurrence of new embolic episodes is essential, because early diagnosis and immediate treatment reduce the risk of a fatal outcome[9]. However, nonspecific clinical presentation and the variety of the suggested diagnosis algorithms, some of which are complex, costly and impractical in all health care scenarios, hinder accurate diagnosis and treatment.

The APE has an incidence of 100 to 200 cases per hundred thousand inhabitants per year[10]. It is important to have a high index of suspicion for the diagnosis, since this disease may be more common than it is considered. Recently, Prandoni *et al.*[11] diagnosed APE in 17.3% of patients admitted for syncope to 11 hospitals in Italy; the frequency of this disorder among individuals who had an alternative diagnosis for syncope was 12.7%.

The death rate associated with the APE is between 5-30%[12], depending on the level of medical care that these patients received; as well as the experience and technical conditions of each center. In patients undergoing surgery for cancer, our group has observed that almost all patients with APE die[8,13]. It is important to point out that only 7% of patients who died prematurely because of an APE is correctly diagnosed[14], indicating the complexity of diagnosing this serious disease and the need to build institutional diagnostic and therapeutic regimens, scientifically designed for the care of patients with suspected APE.

Maestre *et al.*[15] showed that patients who develop a deep vein thrombosis (DVT) or APE at the hospital are at increased risk of death compared to those who develop such disorders in primary health care. Likewise, the risk of bleeding due to treatment is greater in the first group.

In a recent single-center study, Gunter *et al.*[16] observed, when comparing several prognostic scales in patients with APE, that the Acute Physiology and Chronic Health Evaluation II scale was the best to predict mortality at 30 days, followed by the Pulmonary Embolism Severity Index. Therefore, these tools must be routinely and systematically used for adequate risk stratification.

An acute infectious disease, congestive heart failure (CHF) with functional class III/IV, the AMI, acute respiratory, cerebrovascular, rheumatic and inflammatory intestinal diseases, as well as the history of venous thromboembolic disease, eldership, surgery or recent trauma, immobility or paralysis, obesity, central venous catheterization, congenital or acquired thrombophilic states, venous varices and estrogen treatment, are major risk factors for APE in hospitalized patients[17].

When considering the likelihood of developing APE, patients with risk factors can be classified into three groups: high, moderate and low risk (**Tabla 1**)[10]. Therefore, in the individuals of medium and high risk, surveillance and prophylaxis are mandatory.

The most effective and safe measures to prevent the development of DVT and APE, in medical and surgical patients, include:

1. Evaluation and control of risk factors.
2. Early mobilization.
3. Mechanical methods of prevention: compression stockings and graduated pneumatic compression devices.
4. Thromboprofilaxys with anticoagulants: low molecular weight heparin, unfractionated heparin in low dose or fondaparinux in patients without bleeding risk factors (**Tabla 2**)[18,19], in which case the use of mechanical methods is indispensable, especially in high-risk individuals.

In a recent clinical trial of 10010 patients undergoing non-cardiac surgery, the POISE group[20] found that the use of preoperative aspirin, and continued up to 30 days after the operation, did not reduce the risk of DVT or APE; however, a meta-analysis by the same group demonstrated that aspirin reduced perioperative risk of DVT (32108 patients; OR 0.66, 95% CI 0.58-0.75; Cochran's Q test for heterogeneity 4.80; p=0.44; I^2=13%) and APE (36345 patients; OR 0.52, 95% CI 0.33 to 0.80; Cochran's Q test for hete-

Table 1. Risk factors of acute pulmonary embolism in hospitalized patients.

High risk (Odds ratio ≥ 10)	Intermediate risk (Odds ratio 2-9)	Low risk (Odds ratio < 2)
Fracture of long bone (ex. hip, tibia)	Knee arthroscopic surgery	Bed rest > 3 days
Hip or knee replacement surgery	Central venous line	To remain seat (ex. Long journey by car/plane)
Major general surgery	Chemotherapy	Elder
Major trauma	Respiratory/chronic heart failure	Laparoscopic surgery
Spinal cord lesion	Hormonal replacement therapy	Obesity
	Cancer	Venous failure/varicose veins
	Oral contraceptives	
	Immobility due to CVD	
	Pregnancy (peripartum and breastfeeding)	
	Previous venous thrombotic disease	
	Thrombophilia	

CVD, cerebrovascular disease.
Taken and modified from Schellhaa A, *et al.* Dtsch Arztebl Int. 2010;107:589-595[10].

rogeneity 14.72; p=0.005; I^2=73%)[20]. Nevertheless, an increase in the risk of bleeding[20] was also demonstrated; this, added to the high heterogeneity (73%) in studies regarding the benefits on the APE, prevents the widespread use of aspirin in these patients, although it could be considered as a preventive tool in individuals at high risk.

Acute myocardial infarction

The AMI is a potentially fatal disease, typically caused by atherosclerotic coronary obstruction in individuals who are in the community[21]. However, in the hospital environment, the pathophysiological conditions of the AMI may vary; thus, there is a greater proportion of patients with non-atherosclerotic heart attack due to the imbalance among the high metabolic demands of the myocardium and an insufficient blood oxygen supply[6]. However, it is crucial to always keep in mind that many patients who develop this type of AMI do it on previously diseased coronary arteries, which complicates much more the pathophysiological considerations of the disorder and the therapeutic approach and prognosis.

The best scenario for studying the AMI that occurs in the hospital has been in patients with non-cardiac surgery. Approximately in 40% of patients facing such a surgery, the myocardial injury[22] is evident; however, perioperative myocardial infarction is only observed in 5% of individuals[23], with a mortality exceeding the 15%[22].

The perioperative AMI appears usually in the first 72 hours after surgery; generally, it is not associated with the ST segment elevation, and pain is modified by using analgesics, often the opioid types, due to the residual effects of anesthesia and the presence of pain in other regions[24], which requires close monitoring and a high index of suspicion, especially in those patients who develop hypotension, respiratory distress or neurovegetative symptoms. It is also advisable to look for cardiac biomarkers during this period, at least in high-risk individuals.

In patients admitted for medical reasons, the frequency of in-hospital AMI is 5% [25]. In a study where 62021 patients with ST segment elevation AMI were included, Kaul *et al.*[25] found that patients with AMI

Table 2. Risk factors of bleeding in hospitalized patients.

Medical patients [18]	Surgical patients [19]
Active gastroduodenal ulcer	Active bleeding
Bleeding 3 months before admission	Previous major bleeding
Platelet amount < 50 x 10^9/L	Known hemorrhagic non-treated disease
Age ≥ 85 years	Critical hepatic/renal failure
Hepatic failure (INR > 1,5)	Thrombocytopenia
Critical renal failure (TFG < 30 ml/min/m^2)	Acute CVD
Admission to ICU or CCU	Non-monitored hypertension
Central venous catheter	Lumbar puncture / epidural or spinal anesthesia 4 hours before or 12 hours after
Rheumatic disease	Combined use of anticoagulants, antiplatelets or thrombolytics
Current cancer	Abdominal surgery: male sex, preoperative Hb < 13 g/dl, cancer, complex surgery (≥ 2 procedures, difficult dissection or > 1 anastomosis)
Masculine sex	Pancreatoduodenectomy: sepsis, pancreatic leak
	Liver resection: number of segments, concomitant extrahepatic resection, primary liver cancer, preoperative anemia, thrombocytopenia
	Cardiac surgery: aspirin and clopidogrel three days before surgery, overweight/obesity, non-elective surgery, ≥ 5 grafts, elderly
	Chest surgery: pneumonectomy, enlarged resection

CCU, coronary care unit; CVD, cerebrovascular disease; GFR, glomerular filtration rate; Hb, hemoglobine; ICU, intensive care unit; INR, international normalized ratio.

developed in-hospital received treatment of percutaneous coronary intervention less frequently than those who developed it at the community; hence, consequently, they had a mortality significantly higher than that of patients who had an interventional procedure. The lowest mortality was found in those with out-of-hospital AMI[25]. This study shows that patients who have an AMI at the hospital are not offered the same treatment options that the ones with AMI out of the hospital, which is probably related to a poor risk perception of the medical team. Percutaneous coronary intervention in those who develop an AMI at the hospital would reduce cardiac mortality for this cause.

Numerous measures have been suggested to reduce the risk of in-hospital coronary events, usually in patients with non-cardiac surgery[26,27]; nonetheless, no prevention strategy has proven to be effective and safe. In the context of the surgical patient, the following guidelines should be followed:

- Evaluation and control of risk factors.
- To conduct the elective surgery when the patient is in the best possible state of his/her cardiac disease, including the coronary evaluation in high-risk individuals (**Tabla 3**)[27]. In emergency operations, hypotension, hypoxemia, and the acid-base and electrolyte disorders must be corrected as soon as possible –before, during and after entering the operating room– as well as the early use of antibiotics when needed.
- To maintain the base cardiovascular treatment before and after the operation, including the day of the surgery (except antiplatelets and anticoagulants in operations at high risk of bleeding).
- To correct early the acute pathophysiological changes that take place during and after surgery,

such as hypotension, hypoxemia, pain and infections.
- Evaluation and coronary reevaluation, if necessary.

In patients admitted for medical reasons, and in critically ill patients, the same guidelines should be considered as well as avoiding drugs and thrombogenic conditions, and appropriately treat pain, anxiety, sepsis and hypotension.

Acute heart failure

The AHF is a major public health problem and of rapidly growing, responsible for millions of hospitalizations worldwide[28]; it causes a considerable morbidity and its mortality per year ranges from 20 to 30%[29].

The AHF acquired in the hospital is another major cardiovascular problem of the hospitalized patient, about which, little research has been done. In a previous study by our group[8], it was found in 1.9% of patients recently operated, and it represented an independent risk factor of death. The post-infarction AHF appears in 40% of cases; these patients have a higher risk of death at short term, compared to those who do not develop this complication[30].

Different conditions can precipitate an AHF: myocardial ischemia, valvular disease, myocarditis, hypertensive crisis, tachy or bradyarrhythmia, APE, cardiac tamponade, aortic dissection, infections, exacerbation of chronic obstructive pulmonary disease or asthma, anemia, renal failure, adverse drug reactions, excessive ingress of water and salt, thyroid dysfunction and other endocrine disorders[29]. Regardless of the underlying cause, in patients hospitalized some pathophysiological factor that triggers the heart failure is generally present, as during hypoxemia, hypotension, inflammation, increased oxygen consumption or systemic volume overload.

An aspect that is given great importance, due to its frankly iatrogenic nature, is the fluid overload, an aspect to always take into account when treating patients with a previously diseased heart, especially because the energetic fluid contribution is not always justified[31].

Similarly, the hypertensive crisis in hospitalized patients is another factor frequently observed in patients with in-hospital AHF, usually triggered by the suspension of the base antihypertensive treatment or its lack of optimization, overload of water and intravenous salt, or by the use of prohypertensive medications such as corticosteroids[32].

For the prevention of the in-hospital AHF it is suggested:
- Evaluation and control of risk factors.
- To stabilize the patient prior to elective surgery or emergency surgery, including the correction of acute pathophysiological disorders.
- To maintain the base cardiovascular treatment before and after the operation, including the day of surgery (except antiplatelets and anticoagulants in operations at high risk of bleeding) as in patients admitted for medical reasons.
- To correct early acute pathophysiological changes as: hypotension, hypoxemia, pain, acid-base and electrolyte imbalances, anxiety/agitation and infections.
- To avoid the excessive intravenously volume contribution.
- Early mobilization and rehabilitation.
- To prevent/treat renal dysfunction and hypertension.

Cardiorespiratory arrest

The CRA is a frequent event in the in-hospital environment, for which it requires not only a suitably trained staff in cardiopulmonary cerebral resuscitation (CPCR), but also a care system perfectly coordinated and efficient.

In regions where statistics on this type of event are available, such as the United States of America, there are annually reported more than 200 thousand cases of in-hospital CRA[33]; more than 50% occur within the Intensive Care Units[34]. The mortality at discharge is 60-70%[35]; nevertheless, the mortality varies among hospitals and even among areas within the same hospital. In some centers with stringent and efficient CPCR programs it has reduced to 22%[36]. The functional state and the quality of life of the survivals must be considered, because they are frequently affected by neurological damage[37].

Unlike out-of-hospital CRA, that takes place unexpectedly, the one that appears inside the hospital's environment is usually secondary to respiratory dysfunction and shock states, or both[38], with a predictable pathophysiological progression of deterioration before its occurrence. In a recent study, Syue *et al.*[3] observed that only in 36% of patients who pre-

Table 3. Preoperative cardiac risk assessment and perioperative management in the elective surgery*.

Preoperative assessment	Treatment
Active or unstable heart disorder (unstable angina, ACE, significant cardiac arrhythmia, symptomatic valve disease, AMI within the last 30 days or residual myocardial ischemia)	- Multidisciplinary discussion. - If unstable angina and surgery can be postponed, coronary intervention; if unstable angina and surgery cannot be postponed, to optimize medical treatment and operate.
Intermediate/high surgical risk (aortic or vascular surgery, hepatobiliary-pancreatic surgery, esophageal, intraperitoneal, suprarenal and renal, intrathoracic, head and neck, major urological or gynecological surgeries)	- Assessment of functional capacity
Low surgical risk or > 4 MET	- To assess the presence of CRF and indicate changes in lifestyle/medical treatment as appropriate. - ECG if presence of CRF. - Myocardial ischemic disease known: statins and beta blockers at low doses preoperatively. - ICC /systolic dysfunction: preoperative ACE/ARA II. - Vascular surgery: statins.
Intermediate surgical risk and ≤ 4 MET	- To consider noninvasive stress test if presence of CRF.
High surgical risk, ≤ 4 MET and <2 clinical risk factors according to the RCRI (myocardial ischemic disease, AHF, CVD, renal dysfunction, IDDM)	- Echocardiography and biomarkers to assess left ventricular function.
High surgical risk, ≤ 4 MET and ≥ 3 clinical risk factors according to RCRI	- Noninvasive stress test
High surgical risk, ≤ 4 MET and ≥ 3 clinical risk factors according to the RCRI + induced ischemia absent/mild/moderate stress	- To proceed with the planned surgery
High surgical risk, ≤ 4 MET and ≥ 3 clinical risk factors according to the RCRI + induced extensive ischemia in the stress test	- **Box**

* When the surgery is urgent, the strategy will depend on the specific factors of the patient; close monitoring of cardiac events and baseline cardiovascular therapy should be maintained. ARA II, angiotensin-II receptor antagonists; IDDM, insulin-dependent diabetes mellitus; ECG, electrocardiogram; CVD, cerebrovascular disease; CRF, cardiovascular risk factors; CHF, congestive heart failure; AHF, acute heart failure; ACE inhibitors; AMI, acute myocardial infarction; RCRI, revised cardiac risk index; MET, metabolic equivalent. Modified from Kristensen SD, *et al.* Eur J Anaesthesiol. 2014; 31: 517-573[27].

sented an in-hospital CRA it could be identified the cardiac source, indicating that close surveillance should be established, with early, timely, and accurate treatment of any pathophysiological disorder associated with the CRA. The mnemonic device of the five H (hypovolemia, hypoxia, hydrogenions [acidosis], hypo and hyperkalemia, hypothermia) and the five T (Tension pneumothorax, cardiac tamponade, toxics, pulmonary thromboembolism, coronary thrombosis) is an invaluable aid in this context[38].

CONCLUSIONS

Cardiac complications are a frequent cause of death among hospitalized patients. There is insufficient evidence to recommend the routine use of any drug as a preventive measure of these complications,

Box. Treatment of patients at high surgical risk, ≤ 4 MET and ≥ 3 clinical risk factors according to the RCRI, plus extensive induced ischemia in the stress test.

The treatment should be individualized according to the assessment of the risks and benefits according to the proposed surgical intervention.
Coronary artery bypass surgery.
Balloon angioplasty: the operation can be performed after two weeks without discontinuing aspirin therapy.
Metal stent placement: the operation can be performed after four weeks. The double antiplatelet therapy should be maintained for at least four weeks.
Pharmacological stent placement: the operation may be performed in the first six months after placing pharmacological stent of new generation. The operation can be performed in the first twelve months after placing pharmacological stent of older generation.
In each case, the maintenance or temporary suspension of aspirin before surgery must be evaluated, considering the bleeding risk factors of (**Table 2**)

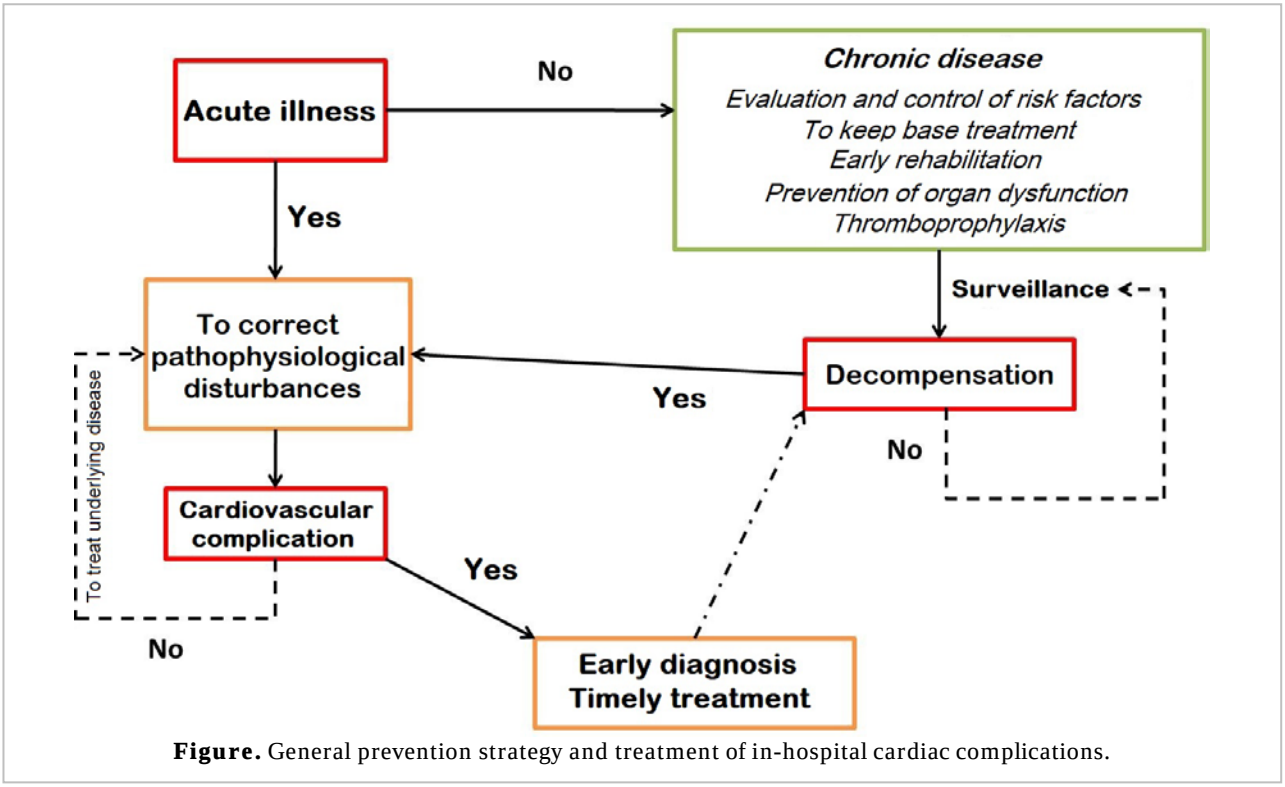

Figure. General prevention strategy and treatment of in-hospital cardiac complications.

except for the thromboprophylaxis in patients with high risk. Adequate clinical trials are required to verify the efficacy and safety of prevention measures.

In the **figure** herein presented is shown a general scheme for the preventive and therapeutic approach for in-hospital cardiac complications. The key is to close monitoring, control and proper correction of acute pathophysiological disorders and underlying disease, early diagnosis of cardiovascular complication, and its energetic and timely treatment.

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