

## The Reduction of Mortality in Acute Myocardial Infarction: From Bed Rest to Future Directions

### Abstract

Despite the reduction of mortality secondary to cardiovascular diseases observed in the last decades, ischemic heart disease remains the most common cause of death worldwide. Among the spectrum of ischemic heart disease, myocardial infarction accounts for most deaths. Since the introduction of the coronary care units in the 1960s, and until the latest antithrombotic drugs, myocardial infarction survival improved by 40–50%. However long-term mortality after myocardial infarction has not improved as short-term mortality. Moreover, the decline of mortality has apparently reached a “plateau” in the past 15 years. In this review we describe the steps of the improvement in ischemic heart disease mortality, from the bed rest to the possible future of treating microcirculation. In fact, coronary artery disease is not only a disease of large vessels that can be visualized with coronary angiography. The small network of pre-arterioles and arterioles that supply the myocardium can be also affected in ischemic heart disease. Thus, despite the introduction of effective recanalization strategies for epicardial coronary arteries such as thrombolysis and, more recently, primary percutaneous intervention, some patients may not achieve effective myocardial reperfusion due to microvascular dysfunction or damage after myocardial infarction. This phenomenon is named no reflow. We believe that no reflow, through the incomplete reperfusion that can account for a higher rate of adverse event in the follow up, should be regarded as one of the open issues in the modern treatment of myocardial infarction.

**Keywords:** *Coronary artery disease, mortality, myocardial infarction, myocardial reperfusion, no reflow, prognosis*

### Introduction

Cardiovascular diseases are the leading cause of death worldwide, being responsible for about 25% of all deaths. Ischemic heart disease (IHD) is the most common presentation among cardiovascular diseases spectrum, and accounts for more than 50% of the mortality.<sup>[1,2]</sup>

Although mortality rates in high income countries have fallen by 40–50% over the past four decades, the burden of morbidity and mortality in IHD remains significant.<sup>[3]</sup>

Among the factors that contributed to the favorable trend in IHD mortality, three played a major role: risk factors modification, improved treatment strategies, and improved secondary prevention strategies.<sup>[4]</sup>

It has been suggested that about 25% of the decline in IHD mortality is due to a decrease in its incidence and nearly 75% is due to a reduction in deaths among patients

with known IHD. Of the latter, about 15% may be ascribed to reductions in mortality from acute presentation of IHD, about 30% to specific medical and surgical treatments for myocardial ischemia, and about 50% to risk factors-directed strategies in patients with known coronary disease.<sup>[5]</sup>

Myocardial infarction (MI) has the greater social impact among IHD. MI accounts for 33% of the total mortality associated with IHD. Indeed, it is estimated that more than 1 million patients in the United States each year experience a first, a recurrent or a silent MI.<sup>[6]</sup>

Along with a reduction of mortality due to IHD, mortality rates after acute MI have improved in the past 40 years as well. Although primary prevention played a role in increasing survival after MI, mostly through a reduced disease severity, the most important contribution was brought by modern and effective treatment strategies.

Short-term mortality (i.e., in-hospital mortality and 30-day mortality) after acute

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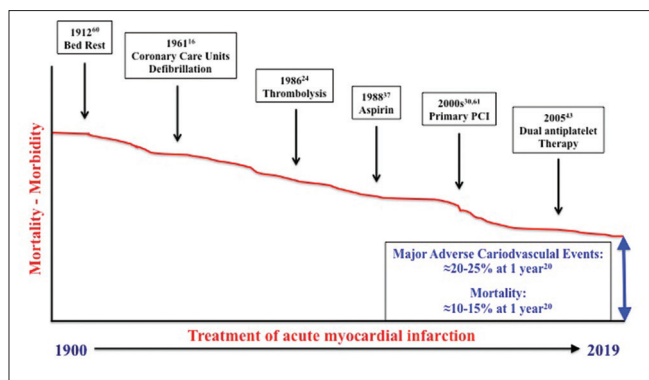
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**Figure 1:** In the last century the morbidity and mortality following myocardial infarction decreased significantly due to the introduction of coronary care units and defibrillations first, and later of reperfusion and antithrombotic strategies

MI had a significant decline, decreasing in absolute terms from more than 30% in the 1950s to an approximate rate of 5–8% nowadays [Figure 1].<sup>[7-10]</sup>

Long-term prognosis has improved in the past decades as well: mortality between 1 month and 1 year from the MI has consistently decreased, and is considered to be around 10–12%.<sup>[9]</sup> Of note, it is slightly higher in patients with non ST-elevation myocardial infarction (NSTEMI) compared to patients with ST-elevation myocardial infarction (STEMI).<sup>[11,12]</sup>

Several advancements have been introduced progressively in the treatment of MI and each of them contributed to the improvement of both short- and long-term prognosis, even though it is challenging to exactly define the precise impact of each innovation.

However, there is increasing evidence that the achievements obtained with short-term mortality have not been as consistent as for long-term mortality. Moreover, it seems that the important decline of MI mortality that has been obtained in the second half of the 20<sup>th</sup> century has progressively reduced, almost reaching a “plateau” in the past 15 years.<sup>[13]</sup>

In this review, we will try to summarize the role of the most important innovations in cardiovascular therapy in the improvement of prognosis, and to understand what is missing to achieve a novel significant reduction in mortality in the treatment of MI.

## The Coronary Care Unit

Before the 1960s there was a lack of specific therapeutic strategies for “heart attack”. Patients with MI (which was a pathologic diagnosis, only confirmed at post-mortem examination) were confined in undisturbed aisles of the hospitals, and the only treatment was total physical and emotional rest for at least six weeks in uncomplicated cases, followed by an even longer period of rest at home.<sup>[14]</sup>

At that time in-hospital mortality reached 30%. Most deaths were secondary to mechanical complications and, more frequently, to fatal arrhythmias.<sup>[15]</sup>

Long-term mortality (i.e., mortality between 1 month and 1 year) was also extremely high: patients surviving the acute phase often developed heart failure (HF), and more than 40% of these patients died due to HF.<sup>[13]</sup>

The development of coronary care units (CCUs), starting from 1961, halved in-hospital mortality, from 30% to around 15%.<sup>[16-18]</sup> The CCU introduced continuous electrocardiogram (ECG) monitoring, the opportunity of ready external defibrillation and cardiac resuscitation. Thus, efficient answers to target the most dreaded complication of MI such as ventricular arrhythmia were introduced.

However, long-term prognosis was still very poor. In fact, the relevant reduction of short-term mortality with the lack of effective reperfusion strategies led to a paradoxical increase of the rate of patients with HF. Pump failure due to extensive myocardial damage and adverse left ventricular remodeling became the principal cause of death, and at least 20% of patients died from HF within 1 year, although there are conflicting data due to the lack of prospective studies in the decade between 1960 and 1970.<sup>[19]</sup>

Thus, reducing the final infarct size became the following goal to improve the prognosis after MI.

## The Reperfusion ERA

Despite pharmacological improvements in the reduction of the MI mortality, most of the improvement in prognosis was probably obtained through the introduction of reperfusion therapies.

The evidence that MI was caused by an abrupt cessation of the blood flow to the myocardium “secondary to sclerotic changes in the coronaries”, as hypothesized in 1879 by the pathologist Ludvig Hektoen, led to the hypothesis that prompt restoration of blood flow could reduce the infarct size by rectifying the imbalance between myocardial oxygen supply and demand.<sup>[20]</sup> Adverse outcome was shown to be directly related to the extension of myocardial damage. Thus, the goal of reperfusion strategies was to reduce the final infarct size.<sup>[21]</sup>

In 1986 the GISSI trial showed that intravenous thrombolytic treatment with streptokinase reduced early mortality in patients with MI by restoring blood flow and reducing the infarct size.<sup>[22]</sup> However, thrombolysis has several complications (mainly major bleeding),<sup>[23]</sup> is effective in restoring blood flow in only 50-60% of the cases<sup>[24]</sup> and, most of all, has not been demonstrated to effectively reduce long-term mortality.<sup>[25]</sup>

Thus, despite the benefits of fibrinolytic therapy over no reperfusion, there are issues of both efficacy and safety that has limited its use. These limitations brought to the introduction of percutaneous strategies to restore blood flow to the myocardium.

Coronary arteriography had already been introduced in 1958 as a diagnostic tool to evaluate vessels anatomy, but the

firsts to describe a transluminal approach to atherosclerotic coronary obstructions were Dotter and Judkins in 1964,<sup>[26]</sup> although Grüntzig is considered the father of percutaneous interventional cardiology in 1979.<sup>[27]</sup>

However, it was not until 1993 that primary percutaneous coronary intervention (PCI) was demonstrated to be superior to fibrinolysis in reducing mortality after MI, setting the foundations for its introduction in clinical practice.<sup>[28]</sup>

The progressive technical improvements, followed by the introduction of the use of coronary stents (first bare-metal stents, and later drug-eluting stents) to reduce the incidence of early reocclusion and late restenosis, have been of essential importance in the reduction of mortality of MI.<sup>[29]</sup>

The benefit of reperfusion strategies were proportionally smaller for long-term compared to short-term prognosis. A large observational study demonstrated that the reduction of short-term mortality after MI decreased by 80% from 1985 to 2008, whereas long-term mortality was reduced only by 40% in the same period.<sup>[30]</sup>

Negative prognosis after MI is mostly due to left ventricular adverse remodeling and, despite significant advances in its treatment, MI remains the most important cause of heart failure (HF).<sup>[21]</sup> Incidence rates of HF after MI remained relatively stable from 1975 to 1991 (around 26%) but decreased thereafter, and today HF after MI develops in approximately 12% of patients.<sup>[31]</sup>

Thrombolysis and PCI have certainly had a fundamental role in the reduction of this complication,<sup>[30,32]</sup> but many studies have shown that reperfusion therapy carries several limitations in improving long-term prognosis.

## Pharmacological Treatment

The introduction of drugs targeted to MI pathogenetic pathways and to the secondary prevention was also a cornerstone in the improvement of the prognosis.

Current treatment of MI encompasses anti-thrombotic therapy, beta-blockers, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), anti-aldosterone drugs and statins.<sup>[33,34]</sup>

The rationale of anti-thrombotic treatment is to counteract the main mechanism of MI, thrombosis of an atherosclerotic plaque. Thus, much effort has been spent trying to find pharmacologic agents that could reverse this phenomenon in the acute phase of MI and prevent future events.

Thrombolysis, as already discussed in the previous paragraph, has been considered the best therapeutic options for around 20 years, before being replaced by PCI.

However other pathways of the thrombosis process have been tried to be addressed in addition to thrombolysis which, through infusion of analogs of tissue plasminogen

activator (tPA), arrest the disease process by breaking down the atherosclerotic clot that occluded the coronary artery.

Anti-platelet drugs, indeed, have been used in the treatment of MI for at least 25 years. The first anti-platelet agent found to be beneficial in the setting of MI was acetylsalicylic acid (ASA), which is now-a-day considered an essential drug for coronary artery disease and is considered the most used medication worldwide.<sup>[35]</sup>

Although the positive effects of ASA had already been suggested in the 1950s and 1960s,<sup>[36]</sup> the first randomized trial to demonstrate the benefit of ASA was the ISIS-2 study, which, back in 1988, showed that the combined use of oral ASA and streptokinase in the setting of acute MI was not only significantly better than either agent alone in reducing 5-week vascular mortality from 13.2% of neither agent to the 8% of both, without increasing serious adverse effects.<sup>[37]</sup>

After the demonstration that treatment with ASA was beneficial, other anti-platelet drugs have been introduced.

Thienopyridines are a class of irreversible ADP receptor/P2Y<sub>12</sub> inhibitors and include ticlopidine, clopidogrel, and prasugrel.

Ticlopidine was not superior to ASA in survivors of MI treated with thrombolysis in the STAMI trial, but adverse effects were slightly higher.<sup>[38]</sup> However, ticlopidine was proven to be beneficial when PCI with stenting was introduced and double antiplatelet treatment became necessary: ASA-ticlopidine treatment reduced the incidence of stent restenosis and stent thrombosis, MI and death, compared with ASA alone or ASA-warfarin.<sup>[39]</sup>

Also clopidogrel, which has similar pharmacological activity to ticlopidine, did not prove to be better than ASA alone after MI.<sup>[40]</sup>

Nonetheless, it has beneficial effects as adjunctive anti-platelet drug: ASA-clopidogrel treatment proved to be superior to ASA-placebo after MI, treated either with thrombolysis or PCI and stent placement, and even in non-reperused patients.<sup>[41-43]</sup>

However, due to the high risk of hematologic side effects, such as neutropenia, bone marrow aplasia and thrombotic thrombocytopenic purpura, ticlopidine is no longer used, and has been replaced by clopidogrel.<sup>[44]</sup>

Although clopidogrel did not prove to be superior to ticlopidine as an adjunctive anti-platelet medication after stent implantation, it produced a 2-fold reduction of adverse effects.<sup>[45]</sup>

Despite the benefits, clopidogrel has substantial issues; the first is that of “resistance” and “non-responsiveness”: a variable proportion of patients – considered between 4% and 30% – treated with conventional doses of clopidogrel do not display adequate antiplatelet response, mostly because

of polymorphisms of the P2Y<sub>12</sub> receptor.<sup>[46]</sup> Moreover, since clopidogrel is a prodrug, it has a delayed effect.<sup>[47]</sup>

Thus, two novel anti-thrombotic medication have been introduced in the past decade, and represent the first therapeutic option after MI treated with PCI and stenting: prasugrel and ticagrelor.

Prasugrel is also a thienopyridine and is a prodrug, but in ex-vivo studies proved to provide inhibition of adenosine diphosphate-induced platelet aggregation more rapidly, more consistently, and to a greater extent than clopidogrel.<sup>[48]</sup> In 2007, the TRITON-TIMI 38 study demonstrated that prasugrel was better than clopidogrel in reducing death, nonfatal MI and nonfatal stroke, despite a slight increase of adverse effects (mainly bleedings). The benefits were absent in patients older than 75 years old, weighing less than 60 kilograms or with history of previous stroke: these, today, are considered contraindications to treatment with prasugrel. However, overall mortality did not differ significantly between treatment groups.<sup>[49]</sup>

Ticagrelor, on the other hand, is not a thienopyridine, and is a reversible, direct-acting inhibitor of the P2Y<sub>12</sub> receptor with a more rapid onset and more pronounced platelet inhibition than clopidogrel.<sup>[50]</sup> The PLATO study compared ticagrelor with clopidogrel in patients with acute coronary syndromes treated with PCI and stenting: the primary end point, a composite of death from vascular causes, MI and stroke, occurred significantly less often in the ticagrelor group than in the clopidogrel group (9.8% of patients vs. 11.7% at 12 months). Moreover, the ticagrelor and clopidogrel group did not differ significantly in the incidence of major bleeding, and, although intracranial bleeding were more frequent, there were fewer episodes of other types of fatal bleeding in the ticagrelor group. The two specific side effects of ticagrelor are non-respiratory dyspnea and ventricular pauses—rarely symptomatic. Finally, mortality from vascular causes with ticagrelor was lower than in patients with clopidogrel (4.0% vs 5.1% at 12 months).

Today, guidelines for both STEMI and NSTEMI suggest to use as a first choice either prasugrel or ticagrelor in adjunction to aspirin in patients undergoing PCI in the acute setting, without giving any preference.<sup>[33,51]</sup>

### The Controversies of Reperfusion Therapy

In 1991 a meta-analysis of studies published between 1960 and 1987 concerning mortality after MI demonstrated that 5-year mortality from the acute event did not significantly decrease after the introduction of thrombolytic therapy. However, when this study was published PCI was not of routine practice.<sup>[52]</sup>

An elegant study published in 2008 demonstrated that despite long-term outcome after MI had improved by 3% per

year in the previous 10 years, after adjustment for the use of pharmacological therapy the trend in post-MI outcome improvement was completely abolished. This indicated that improved long-term outcome was due to the introduction of an effective secondary prevention pharmacologic strategy. In addition, although there was evidence that MI-related PCI procedures also may have contributed to improved survival, after adjusting for MI-related PCI procedural use during the index MI hospitalization, the temporal change associated with improved prognosis was largely attenuated. This suggests that improvement in short-term outcomes may have been attributable to PCI, whereas evidence-based secondary prevention therapies provided significant long-term prognostic benefit.<sup>[53]</sup>

Moreover, a Danish study showed that mortality between month 1 and 12 declined from 15.6% to 11.1% from 1984 to 2008, whereas first-month mortality improved more consistently from 31.4% to 14.8%.<sup>[54]</sup>

In the first trials comparing PCI and fibrinolysis in 1993 left ventricular function after MI was comparable among the two reperfusion strategies. Since long-term prognosis mainly depends upon left ventricular function, this might explain the different improvements achieved in short- vs mid- and long-term prognosis.<sup>[28]</sup>

This data suggest that the introduction of reperfusion strategies doubtlessly had a fundamental role in the outstanding improvement of prognosis of acute MI, but this beneficial effect might be confined to short-term outcome, as if in some patients, the advantage of reperfusion would not be that consistent.

### What is Missing? The Role of Microcirculation

One possible explanation could be that interventional reperfusion strategies have the aim of restoring the overtly visible interruption of blood flow supplying the heart muscle but are incapable on acting on what happens “inside” the myocardium during myocardial infarction.

Coronary artery disease is not only a disease of big vessels, which are the one that can be visualized at coronary arteriography, but also a disease of the coronary microcirculation.

In 1993, Lincoff and Topol provocatively wondered if reperfusion (with thrombolytic therapy) was just an illusion and they underlined that there could be a dissociation between infarct artery patency and myocardial tissue reperfusion.<sup>[55]</sup>

This discrepancy could be due to coronary artery incomplete patency and reocclusion but also, and maybe mostly, to altered microcirculatory function.

Thus, microcirculation impairment might have a fundamental negative prognostic role that, today, lacks of therapeutic targets and might be responsible for the



‘plateau’ of the improvement of prognosis after myocardial infarction in the past 5–10 years.

Back in 1974, Kloner, demonstrated in dogs that, after occluding a coronary artery for 90 minutes, reperfusion (assessed by injecting two fluorescent tracers, i.e. thioflavin S and carbon black) did not occur homogeneously in the myocardium distal to the occlusion. This study shows that restoring the coronary artery patency does not imply a recovery of perfusion.<sup>[56]</sup>

This phenomenon, named no reflow (NR), was then demonstrated in humans and defined as an inadequate myocardial reperfusion after coronary revascularization through thrombolysis or PCI in the setting of an acute MI.

Being responsible of an incomplete reperfusion, NR might nowadays be considered one of the main responsible of long-term cardiac dysfunction and mortality.<sup>[57,58]</sup>

## Conclusions

The treatment of MI has improved significantly in the last decades and, consequently, also prognosis improved significantly. However, the reduction of adverse events has reached a steady-state and in the last years it has not improved significantly. Future management of MI should probably focus on patients with a suboptimal reperfusion, since this subset carries a higher risk of death, and may need more aggressive therapeutic approach, together with stricter follow-up in order to reduce the onset of long-term complications.

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