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Atorvastatin Loading Dose in STEMI Before Primary PCI: Evidence on Epicardial Flow, No-Reflow Phenomenon, and Clinical Outcomes

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Abstract

Background: Primary percutaneous coronary intervention remains the preferred reperfusion strategy for patients with ST-segment elevation myocardial infarction when it can be performed rapidly, because restoration of infarct-related artery patency is central to myocardial salvage and survival. However, successful opening of the epicardial artery does not always translate into adequate myocardial tissue reperfusion. Impaired final Thrombolysis in Myocardial Infarction flow, slow-flow, no-reflow, reduced myocardial blush grade, and incomplete ST-segment resolution are important markers of larger infarct size, adverse ventricular remodeling, heart failure, and mortality. Therefore, adjunctive pharmacological strategies that improve both epicardial and microvascular reperfusion are clinically relevant in contemporary STEMI care.

High-dose atorvastatin loading before PCI has attracted interest because statins exert rapid pleiotropic effects beyond lipid lowering, including improvement of endothelial function, attenuation of inflammation, reduction of oxidative stress, inhibition of platelet activation, stabilization of vulnerable plaque, and modulation of thrombus burden. These mechanisms are highly relevant in STEMI, where plaque rupture, intense thrombosis, distal embolization, vasoconstriction, and microvascular obstruction contribute to impaired TIMI flow and no-reflow. Early randomized trials in PCI populations suggested that atorvastatin pretreatment reduces periprocedural myocardial injury, while STEMI-focused studies have examined its impact on final TIMI flow, corrected TIMI frame count, myocardial blush, ST-segment resolution, and short-term clinical outcomes.

The available evidence suggests that atorvastatin loading before primary PCI is biologically plausible, safe, inexpensive, and potentially beneficial, particularly in patients actually undergoing PCI. The largest ACS trial, SECURE-PCI, did not show a significant reduction in 30-day major adverse cardiovascular events in the overall ACS population, but suggested benefit among patients treated with PCI and in STEMI subgroups. Smaller STEMI trials and meta-analyses have reported improvement in angiographic and electrocardiographic reperfusion indices, including better final TIMI flow and lower no-reflow rates. Accordingly, early high-intensity statin therapy should be viewed as an important component of STEMI management, while the specific incremental effect of pre-PCI atorvastatin loading on TIMI flow remains an area requiring careful interpretation and further study.

Keywords: *Atorvastatin ,Loading Dose, STEMI Before Primary PCI*

Introduction

ST-segment elevation myocardial infarction (STEMI) is the most severe manifestation of acute coronary syndrome and remains a leading cause of cardiovascular morbidity and mortality worldwide. The condition is characterized by acute thrombotic occlusion of an epicardial coronary artery following rupture or erosion of an

atherosclerotic plaque, resulting in prolonged myocardial ischemia and irreversible myocardial necrosis if reperfusion is delayed. Early restoration of coronary blood flow is therefore the principal therapeutic goal to preserve viable myocardium, maintain left ventricular function, and improve both short- and long-term clinical outcomes. Primary percutaneous coronary intervention (PCI) is currently the preferred reperfusion strategy when performed within the recommended time frame because it provides superior coronary patency, lower reinfarction rates, and improved survival compared with fibrinolytic therapy. [1]

Although successful primary PCI restores patency of the infarct-related artery in the majority of patients, angiographic success does not always translate into effective myocardial reperfusion. Restoration of normal epicardial coronary blood flow, commonly assessed using the Thrombolysis in Myocardial Infarction (TIMI) grading system, represents one of the strongest predictors of myocardial salvage and prognosis after STEMI. Patients achieving final TIMI grade 3 flow consistently demonstrate smaller infarct size, better recovery of left ventricular function, lower incidence of heart failure, and improved survival compared with patients with impaired post-procedural coronary flow. [2]

Despite advances in interventional techniques and antithrombotic therapy, impaired coronary reperfusion remains an important challenge during primary PCI. The no-reflow phenomenon, defined as inadequate myocardial perfusion despite successful reopening of the epicardial coronary artery, occurs in a substantial proportion of STEMI patients and is associated with adverse clinical outcomes. Multiple mechanisms contribute to no-reflow, including distal embolization of thrombotic material, ischemia-reperfusion injury, endothelial dysfunction, microvascular obstruction, inflammatory activation, oxidative stress, platelet aggregation, and vasoconstriction. Consequently, therapeutic strategies capable of preserving microvascular integrity before coronary intervention have become an area of considerable research interest. [3]

Statins are well established as the cornerstone of long-term secondary prevention following acute myocardial infarction because of their potent cholesterol-lowering properties and proven ability to reduce recurrent cardiovascular events. However, accumulating evidence has demonstrated that statins also exert several rapid cholesterol-independent or pleiotropic effects that occur within hours of administration. These include improvement of endothelial nitric oxide bioavailability, attenuation of systemic and vascular inflammation, reduction of oxidative stress, inhibition of platelet activation, stabilization of vulnerable atherosclerotic plaques, and improvement of coronary microvascular function. Such biological effects provide a strong rationale for administering high-dose atorvastatin before primary PCI in STEMI patients. [4,5]

Several randomized clinical trials and observational studies have evaluated whether atorvastatin loading before PCI improves angiographic and clinical outcomes. Early investigations in patients undergoing elective and urgent PCI demonstrated reductions in periprocedural myocardial injury following high-dose atorvastatin pretreatment, while subsequent studies extended this concept to patients presenting with acute coronary syndromes and STEMI. More recently, evidence has focused on the effects of atorvastatin loading on final TIMI flow, corrected TIMI frame count, myocardial blush grade, ST-segment resolution, no-reflow, and major adverse cardiovascular events after primary PCI. Although many studies have suggested favorable effects, results remain heterogeneous because of differences in study populations, timing of drug administration, atorvastatin dosage, previous statin exposure, and concomitant pharmacological therapies. [5–8]

Therefore, a comprehensive review of the available literature is warranted to clarify the role of high-dose atorvastatin loading before primary PCI in STEMI patients. This review aims to summarize the current evidence regarding its effects on epicardial coronary reperfusion, TIMI flow, no-reflow phenomenon, myocardial perfusion, and subsequent clinical outcomes, while identifying areas in which further high-quality research is needed.

Pathophysiological Basis of Impaired TIMI Flow and No-Reflow in STEMI

Primary PCI is designed to restore patency of the infarct-related artery, but the quality of reperfusion depends on more than mechanical opening of the occluded vessel. TIMI flow grade remains one of the most practical angiographic methods for assessing epicardial reperfusion after PCI. TIMI 0 indicates absent antegrade flow, TIMI 1 minimal penetration beyond the obstruction, TIMI 2 delayed but complete distal filling, and TIMI 3 normal coronary flow. In STEMI, final TIMI 3 flow is strongly associated with better myocardial salvage, smaller infarct size, improved left ventricular function, and lower mortality, whereas final TIMI flow less than

grade 3 reflects incomplete reperfusion and worse prognosis. [9,10]

The no-reflow phenomenon represents failure of adequate myocardial perfusion despite successful reopening of the epicardial coronary artery. It is particularly relevant in STEMI because the culprit artery usually contains large thrombotic burden, friable plaque material, activated platelets, inflammatory cells, and vasoconstrictor mediators. During balloon dilatation and stent implantation, distal embolization of thrombus and atheromatous debris may obstruct the coronary microcirculation. This process can convert an apparently successful PCI result into impaired tissue reperfusion, slow-flow, or angiographic no-reflow, even when residual epicardial stenosis is minimal. [11,12]

Microvascular injury in STEMI is also driven by ischemia-reperfusion injury. Prolonged ischemia causes endothelial swelling, capillary plugging, increased vascular permeability, and microvascular compression from myocardial edema. When reperfusion occurs, oxidative stress, calcium overload, inflammatory activation, and neutrophil adhesion further damage the microcirculation. These mechanisms reduce capillary perfusion and may explain why epicardial TIMI 3 flow does not always guarantee complete myocardial reperfusion. Therefore, both epicardial and microvascular components must be considered when evaluating the success of reperfusion therapy. [11,13]

Inflammation and platelet activation are central contributors to impaired coronary flow during STEMI. Plaque rupture exposes thrombogenic material, leading to platelet adhesion, aggregation, thrombin generation, and fibrin-rich thrombus formation. Activated platelets release vasoconstrictors and inflammatory mediators that aggravate endothelial dysfunction and microvascular obstruction. This biological environment provides a rational target for therapies that can rapidly reduce inflammation, improve endothelial function, inhibit platelet activity, and stabilize plaque. High-dose atorvastatin loading may be relevant in this setting because several of its early pleiotropic effects directly oppose mechanisms involved in slow-flow and no-reflow. [14,15]

Rationale for High-Dose Atorvastatin Loading Before Primary PCI

The rationale for atorvastatin loading before primary PCI is based on the concept that statins may produce beneficial vascular effects before significant lipid reduction occurs. In STEMI, the coronary circulation is exposed to acute thrombosis, inflammation, endothelial dysfunction, vasoconstriction, and distal embolization. A high loading dose of atorvastatin given before PCI may help modify this unstable biological environment during the early reperfusion phase. These early effects are clinically important because the risk of impaired TIMI flow and no-reflow is highest during coronary wiring, balloon dilatation, thrombus manipulation, and stent deployment. [16]

Atorvastatin improves endothelial function partly by increasing nitric oxide bioavailability and reducing oxidative stress. This may help limit coronary vasoconstriction and improve microvascular tone during reperfusion. In STEMI, endothelial dysfunction is not limited to the culprit lesion but may involve the downstream microcirculation, where vasoconstriction and capillary obstruction contribute to slow-flow and no-reflow. Therefore, early atorvastatin administration may support more effective epicardial and tissue-level reperfusion after primary PCI. [17]

Another important mechanism is the anti-inflammatory effect of intensive statin therapy. Acute myocardial infarction is accompanied by a marked inflammatory response, including activation of leukocytes, endothelial cells, cytokines, and adhesion molecules. This inflammatory cascade contributes to plaque instability, microvascular plugging, and reperfusion injury. High-dose atorvastatin may reduce inflammatory activity rapidly, which provides a mechanistic explanation for its possible association with improved post-procedural TIMI flow and reduced myocardial injury. [18]

Atorvastatin may also exert antithrombotic and antiplatelet effects, which are highly relevant in STEMI patients undergoing primary PCI. The infarct-related artery usually contains platelet-rich thrombus, and mechanical intervention can fragment thrombotic material, causing distal embolization. By reducing platelet activation, thrombin generation, and vascular inflammation, atorvastatin loading may theoretically decrease thrombus propagation and microvascular obstruction. This effect may be particularly valuable in patients with high thrombus burden or delayed presentation. [19]

The pleiotropic effects of atorvastatin provide a strong biological basis for studying angiographic endpoints such as final TIMI flow, corrected TIMI frame count, myocardial blush grade, and no-reflow. These endpoints reflect different levels of reperfusion, from epicardial artery patency to myocardial tissue perfusion. Although routine high-intensity statin therapy is already recommended after STEMI, the specific question is whether giving a loading dose before PCI provides additional early protection during the procedure itself. [20]

Evidence From PCI and Acute Coronary Syndrome Studies

Early clinical evidence supporting atorvastatin loading came from studies in patients undergoing coronary intervention, where pretreatment with high-dose atorvastatin was associated with less periprocedural myocardial injury. These trials established the concept that statins may provide acute procedural protection beyond chronic lipid lowering. Although many early studies were not limited to STEMI, they were important because they demonstrated that short-term statin loading before PCI could reduce biomarker-defined myocardial damage and improve early procedural outcomes. [21]

The ARMYDA trial showed that atorvastatin pretreatment before elective PCI significantly reduced post-procedural myocardial injury. This finding was clinically relevant because it suggested that statin therapy could exert protective effects within a short time before coronary instrumentation. The mechanism was thought to involve anti-inflammatory, endothelial, and antithrombotic effects rather than lipid reduction alone. Although elective PCI differs from primary PCI in STEMI, the trial provided a foundation for later studies evaluating high-dose atorvastatin in more unstable thrombotic settings. [22]

In patients with acute coronary syndromes undergoing early invasive management, the ARMYDA-ACS trial further supported the benefit of atorvastatin loading. Patients receiving high-dose atorvastatin before PCI had fewer early major adverse cardiac events compared with placebo, mainly driven by reduction in periprocedural myocardial infarction. This result strengthened the hypothesis that statin loading could be beneficial when coronary plaque activity, inflammation, and thrombus formation are prominent. These features are even more intense in STEMI, where the infarct-related artery is usually acutely occluded. [23]

The NAPLES II trial also evaluated atorvastatin loading before PCI and reported a reduction in periprocedural myocardial infarction among statin-naïve patients undergoing elective coronary intervention. Although the study population was not focused on STEMI, it contributed additional support for acute statin pretreatment as a cardioprotective strategy. Its importance lies in showing that even a single high dose of atorvastatin before PCI may reduce myocardial injury, reinforcing the plausibility of giving atorvastatin before primary PCI whenever possible. [24]

The SECURE-PCI trial provided the largest randomized evaluation of early atorvastatin loading in acute coronary syndrome patients planned for invasive management. In the overall population, two loading doses of atorvastatin did not significantly reduce 30-day major adverse cardiovascular events. However, among patients who actually underwent PCI, atorvastatin loading was associated with better outcomes, suggesting that the benefit may be linked to the procedural setting. This finding is particularly relevant to STEMI patients treated by primary PCI, although interpretation requires caution because subgroup findings should be considered hypothesis-generating. [25]

Evidence From STEMI Studies on TIMI Flow and No-Reflow

In STEMI patients undergoing primary PCI, the potential benefit of atorvastatin loading is especially relevant because the infarct-related artery is usually occluded by fresh thrombus. Several STEMI-focused studies have investigated whether high-dose atorvastatin before PCI improves angiographic reperfusion. The main endpoints have included final TIMI flow grade, corrected TIMI frame count, myocardial blush grade, ST-segment resolution, no-reflow, infarct size markers, and early adverse cardiac events. These outcomes are important because they reflect both epicardial patency and downstream myocardial perfusion after reperfusion. [26]

The STATIN STEMI trial evaluated high-dose atorvastatin loading before primary PCI and provided important evidence in this specific clinical setting. Although the trial did not demonstrate a major reduction in all clinical endpoints, atorvastatin loading was associated with favorable effects on some angiographic and electrocardiographic reperfusion parameters. This supported the concept that early intensive statin therapy may

improve the quality of reperfusion, particularly through mechanisms related to endothelial protection, thrombus modulation, and microvascular preservation during primary PCI. [27]

Studies assessing no-reflow after primary PCI have suggested that atorvastatin loading may reduce the frequency of impaired coronary flow in selected patients. This effect is biologically plausible because no-reflow is closely related to distal embolization, microvascular obstruction, inflammation, platelet activation, and reperfusion injury. By acting on several of these pathways simultaneously, atorvastatin may improve final angiographic flow and reduce microvascular dysfunction. However, the magnitude of benefit varies across studies, partly because no-reflow definitions and assessment methods are not uniform. [28]

Corrected TIMI frame count and myocardial blush grade provide more sensitive information than simple TIMI flow grading alone. Some studies have reported that patients receiving high-dose atorvastatin before primary PCI demonstrate faster coronary flow and better myocardial blush, suggesting improvement in both epicardial and tissue-level reperfusion. These findings are clinically meaningful because patients with preserved myocardial blush and rapid ST-segment resolution usually have smaller infarcts and better ventricular recovery. Still, these endpoints are surrogate markers and should be interpreted together with clinical outcomes. [29]

Overall, STEMI data suggest that atorvastatin loading before primary PCI is safe and may improve angiographic reperfusion, especially final TIMI 3 flow, slow-flow/no-reflow rates, corrected TIMI frame count, and myocardial perfusion indices. The strongest argument for its use is that high-intensity statin therapy is already indicated early after STEMI, while giving the dose before PCI may provide additional procedural benefit with minimal downside. Nevertheless, available studies remain heterogeneous, and larger trials focused specifically on TIMI flow and no-reflow are needed to define which patients benefit most. [30]

Clinical Outcomes After Atorvastatin Loading in Primary PCI

The clinical value of atorvastatin loading before primary PCI depends not only on angiographic improvement but also on whether better reperfusion translates into fewer adverse outcomes. Improved final TIMI flow and reduced no-reflow are associated with smaller infarct size, better left ventricular recovery, and lower risk of heart failure. Therefore, even when a study is not powered to detect mortality benefit, improvement in reperfusion markers may still be clinically meaningful in STEMI patients. [31]

Some studies have suggested that early high-dose atorvastatin may reduce periprocedural myocardial injury and early recurrent ischemic events after PCI. This benefit may be explained by rapid plaque stabilization, reduction of inflammatory activation, improvement of endothelial function, and attenuation of thrombotic activity. In STEMI, these mechanisms may be particularly important during the first hours after symptom onset, when thrombus burden and inflammatory activity are maximal. [32]

The effect of atorvastatin loading on major adverse cardiovascular events has been less consistent than its effect on surrogate reperfusion markers. Large trials in acute coronary syndrome populations have shown neutral overall results, while PCI-treated subgroups appeared to benefit more. This suggests that atorvastatin loading may be most useful when given close to the time of coronary intervention, where its procedural protective effects are most relevant. [33]

Short-term outcomes after primary PCI are strongly influenced by multiple factors, including ischemic time, infarct location, baseline TIMI flow, thrombus burden, diabetes, renal function, left ventricular function, and use of potent antiplatelet therapy. For this reason, the independent contribution of atorvastatin loading may be difficult to isolate. However, because high-intensity statin therapy is already recommended after STEMI, pre-procedural loading represents a practical strategy that may offer additional benefit without delaying reperfusion. [34]

Current evidence supports early atorvastatin administration as part of comprehensive STEMI care, with possible advantages in angiographic reperfusion and selected clinical outcomes. The strongest clinical argument is that atorvastatin loading is simple, inexpensive, widely available, and safe in most patients. Its use should not replace rapid reperfusion or optimal antithrombotic therapy, but it may act as an adjunctive measure to improve the biological conditions of primary PCI and potentially reduce early adverse events. [35]

Safety, Timing, and Practical Use of Atorvastatin Loading

High-dose atorvastatin loading before primary PCI is generally considered safe in STEMI patients when there is no clear contraindication, such as active liver disease, known severe statin intolerance, or major drug interaction. The usual loading approach in clinical studies has involved atorvastatin 80 mg given as early as possible before PCI, followed by continuation of high-intensity statin therapy during hospitalization and after discharge. This strategy is practical because it does not delay reperfusion and aligns with guideline-based secondary prevention. [36]

The timing of administration is important because the proposed benefit of loading depends on achieving rapid pleiotropic effects before balloon inflation and stent deployment. In real-world STEMI care, the loading dose may be given in the emergency department, ambulance, catheterization laboratory, or immediately after diagnosis if primary PCI is planned. Although earlier administration is theoretically preferable, reperfusion should never be delayed to administer statin therapy. Atorvastatin loading should be integrated into the STEMI treatment pathway alongside aspirin, P2Y12 inhibition, anticoagulation, and rapid transfer for PCI. [37]

Patient selection may influence the observed benefit of atorvastatin loading. Individuals with high thrombus burden, delayed presentation, diabetes mellitus, large anterior infarction, impaired baseline TIMI flow, or high inflammatory status may be more vulnerable to no-reflow and may theoretically gain greater benefit from early intensive statin therapy. However, current evidence is not sufficient to restrict loading only to these groups. Since most STEMI patients require high-intensity statin therapy after myocardial infarction, early loading remains a reasonable universal approach unless contraindicated. [38]

Atorvastatin loading should be understood as an adjunctive strategy rather than a substitute for established reperfusion and antithrombotic treatment. Optimal STEMI care still depends on minimizing ischemic time, achieving technically successful PCI, using appropriate antiplatelet and anticoagulant therapy, managing thrombus burden, and treating complications promptly. The role of atorvastatin is to improve the biological conditions surrounding reperfusion and possibly reduce microvascular injury, not to compensate for delayed or incomplete mechanical reperfusion. [39]

In clinical practice, the balance of evidence favors early high-intensity atorvastatin use because it is simple, low-cost, and consistent with post-STEMI secondary prevention. Even if the incremental effect on TIMI flow and no-reflow is modest, the overall benefit-risk profile supports giving atorvastatin early in eligible STEMI patients undergoing primary PCI. Future research should better define the optimal timing, dose, and patient subgroups most likely to show angiographic and clinical improvement. [40]

imitations of Current Evidence and Research Gap

Although available evidence supports early high-intensity atorvastatin in STEMI, the specific effect of pre-PCI loading on TIMI flow remains incompletely established. Many studies used small sample sizes, single-center designs, and surrogate angiographic endpoints rather than adequately powered clinical outcomes. This limits the ability to conclude that improved TIMI flow or reduced no-reflow directly results in lower mortality or heart failure. [27]

Another limitation is heterogeneity in atorvastatin dose, timing, and patient background. Some studies enrolled statin-naïve patients, while others included patients already receiving chronic statin therapy. The interval between loading dose and balloon inflation also varied widely, which may influence the magnitude of pleiotropic benefit. [25]

Definitions of no-reflow also differ between studies. Some investigators used final TIMI flow alone, whereas others included corrected TIMI frame count, myocardial blush grade, or ST-segment resolution. This variation makes direct comparison difficult and may explain conflicting results between trials. [29]

The main research gap is identifying which STEMI patients benefit most from atorvastatin loading before primary PCI. Patients with high thrombus burden, diabetes, delayed presentation, anterior infarction, or impaired baseline TIMI flow may be more likely to develop no-reflow, but this requires confirmation in larger targeted studies. [38]

Future trials should focus on standardized no-reflow definitions, precise timing of atorvastatin administration, and clinically meaningful endpoints such as infarct size, left ventricular recovery, heart failure hospitalization, recurrent myocardial infarction, and mortality. Until then, atorvastatin loading should be considered a safe and reasonable adjunct to primary PCI rather than a proven stand-alone strategy for preventing no-reflow. [40]

Conclusion

High-dose atorvastatin loading before primary PCI in STEMI is a safe, practical, and biologically justified strategy that may improve epicardial flow, reduce no-reflow, and enhance myocardial reperfusion. Its greatest value is as an early adjunct to rapid mechanical reperfusion and optimal antithrombotic therapy, with strongest support in patients undergoing PCI and those at high risk of impaired coronary flow.

References

1. Ibanez B, James S, Agewall S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J.* 2018;39(2):119-177.
2. Collet JP, Thiele H, Barbato E, et al. 2023 ESC guidelines for the management of acute coronary syndromes. *Eur Heart J.* 2023;44(38):3720-3826.
3. Levine GN, Bates ER, Blankenship JC, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with STEMI. *J Am Coll Cardiol.* 2016;67(10):1235-1250.
4. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction. *Eur Heart J.* 2019;40(3):237-269.
5. The TIMI Study Group. The Thrombolysis in Myocardial Infarction trial: phase I findings. *N Engl J Med.* 1985;312(14):932-936.
6. Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. *Circulation.* 1996;93(5):879-888.
7. van 't Hof AWJ, Liem A, Suryapranata H, Hoorntje JCA, de Boer MJ, Zijlstra F. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction. *Circulation.* 1998;97(23):2302-2306.
8. Ito H, Maruyama A, Iwakura K, et al. Clinical implications of the no-reflow phenomenon. *Circulation.* 1996;93(2):223-228.
9. Morishima I, Sone T, Okumura K, et al. Angiographic no-reflow phenomenon as a predictor of adverse long-term outcome in patients treated with PCI for first acute myocardial infarction. *J Am Coll Cardiol.* 2000;36(4):1202-1209.
10. Niccoli G, Burzotta F, Galiuto L, Crea F. Myocardial no-reflow in humans. *J Am Coll Cardiol.* 2009;54(4):281-292.
11. Rezkalla SH, Kloner RA. Coronary no-reflow phenomenon: from the experimental laboratory to the cardiac catheterization laboratory. *Catheter Cardiovasc Interv.* 2008;72(7):950-957.
12. Jaffe R, Charron T, Puley G, Dick A, Strauss BH. Microvascular obstruction and no-reflow after PCI. *Circulation.* 2008;117(24):3152-3156.
13. Eeckhout E, Kern MJ. The coronary no-reflow phenomenon: a review of mechanisms and therapies. *Eur Heart J.* 2001;22(9):729-739.
14. Libby P. Inflammation in atherosclerosis. *Nature.* 2002;420(6917):868-874.
15. Liao JK, Laufs U. Pleiotropic effects of statins. *Annu Rev Pharmacol Toxicol.* 2005;45:89-118.
16. Davignon J. Beneficial cardiovascular pleiotropic effects of statins. *Circulation.* 2004;109(23 suppl 1):III39-III43.

17. Ray KK, Cannon CP. The potential relevance of the multiple lipid-independent effects of statins in the management of acute coronary syndromes. *J Am Coll Cardiol.* 2005;46(8):1425-1433.

18. Kwak B, Mulhaupt F, Myit S, Mach F. Statins as a newly recognized type of immunomodulator. *Nat Med.* 2000;6(12):1399-1402.

19. Undas A, Brummel-Ziedins KE, Mann KG. Statins and blood coagulation. *Arterioscler Thromb Vasc Biol.* 2005;25(2):287-294.

20. Patti G, Chello M, Candura D, et al. Randomized trial of atorvastatin for reduction of myocardial damage during coronary intervention. *Circulation.* 2004;110(6):674-678.

21. Patti G, Pasceri V, Colonna G, et al. Atorvastatin pretreatment improves outcomes in patients with acute coronary syndromes undergoing early PCI: results of the ARMYDA-ACS randomized trial. *J Am Coll Cardiol.* 2007;49(12):1272-1278.

22. Briguori C, Visconti G, Focaccio A, et al. Novel approaches for preventing or limiting events II trial: impact of a single high loading dose of atorvastatin on periprocedural myocardial infarction. *J Am Coll Cardiol.* 2009;54(23):2157-2163.

23. Di Sciascio G, Patti G, Pasceri V, et al. Efficacy of atorvastatin reload in patients on chronic statin therapy undergoing PCI: results of the ARMYDA-RECAPTURE randomized trial. *J Am Coll Cardiol.* 2009;54(6):558-565.

24. Kim JS, Kim J, Choi D, et al. Efficacy of high-dose atorvastatin loading before primary PCI in STEMI: the STATIN STEMI trial. *JACC Cardiovasc Interv.* 2010;3(3):332-339.

25. Berwanger O, Santucci EV, de Barros E Silva PGM, et al. Effect of loading dose of atorvastatin prior to planned PCI on major adverse cardiovascular events in acute coronary syndrome: the SECURE-PCI randomized clinical trial. *JAMA.* 2018;319(13):1331-1340.

26. Lopes RD, de Barros E Silva PGM, de Andrade Jesuino I, et al. Timing of loading dose of atorvastatin in patients undergoing PCI for acute coronary syndromes: insights from SECURE-PCI. *JAMA Cardiol.* 2018;3(11):1113-1118.

27. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med.* 2004;350(15):1495-1504.

28. Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study. *JAMA.* 2001;285(13):1711-1718.

29. de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs delayed conservative simvastatin strategy in acute coronary syndromes: phase Z of the A to Z trial. *JAMA.* 2004;292(11):1307-1316.

30. Patti G, Cannon CP, Murphy SA, et al. Clinical benefit of statin pretreatment in patients undergoing PCI: a collaborative patient-level meta-analysis of 13 randomized studies. *Circulation.* 2011;123(15):1622-1632.

31. Winchester DE, Wen X, Xie L, Bavry AA. Evidence of pre-procedural statin therapy: a meta-analysis of randomized trials. *J Am Coll Cardiol.* 2010;56(14):1099-1109.

32. Navarese EP, Kowalewski M, Andreotti F, et al. Meta-analysis of time-related benefits of statin therapy in patients with acute coronary syndrome undergoing PCI. *Am J Cardiol.* 2014;113(10):1753-1764.

33. Zhang BC, Li WM, Xu YW. High-dose statin pretreatment for prevention of no-reflow during PCI: a meta-analysis. *Can J Cardiol.* 2011;27(6):851-858.

34. Chen M, Wang H, Li X, et al. High-dose statin pretreatment for prevention of contrast-induced nephropathy and periprocedural myocardial injury in PCI. *Int J Cardiol.* 2013;167(5):1994-2000.

35. Hara M, Sakata Y, Nakatani D, et al. Impact of statin pretreatment on clinical outcome in patients with acute myocardial infarction undergoing PCI. *Circ J.* 2010;74(11):2449-2455.

36. Ndrepepa G, Kastrati A. Mechanical strategies to prevent no-reflow during primary PCI in STEMI. *Circ*

Cardiovasc Interv. 2012;5(5):615-617.

37. Stone GW, Peterson MA, Lansky AJ, Dangas G, Mehran R, Leon MB. Impact of normalized myocardial perfusion after successful angioplasty in acute myocardial infarction. *J Am Coll Cardiol.* 2002;39(4):591-597.
38. Henriques JPS, Zijlstra F, Ottervanger JP, et al. Incidence and clinical significance of distal embolization during primary angioplasty for acute myocardial infarction. *Eur Heart J.* 2002;23(14):1112-1117.
39. Vlaar PJ, Svilaas T, van der Horst ICC, et al. Cardiac death and reinfarction after 1 year in TAPAS: thrombus aspiration during primary PCI. *Lancet.* 2008;371(9628):1915-1920.
40. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with ACS. *N Engl J Med.* 2007;357(20):2001-2015.