Journal of Environmental Science [JES] https://jesj.journals.ekb.eg/
An International Journal **doi:** *10.21608/JESJ.2022.181114.1035*

Timing of post thrombolysis PCI in acute MI

Alshimaa Lotfy Hamed*
Department of internal medicine and cardiology, Faculty of medicine, Sohag University- 82524, Sohag, Egypt

Citation: *Hamed, A. L. (2022). Timing of post thrombolysis PCI in acute MI, Vol. 28(1): 48-55.*

Article Information
Received 15 December. 2022,
Revised 19 December 2022,
Accepted 21 December 2022.
Published online 30 December 2022.

Abstract: The cardiovascular disease spectrum includes acute myocardial infarction, which enlarges the ongoing problem for the global health care delivery system. Many non-PCI medical facilities throughout the world continue to use pharmacoinvasive strategies as their first line of treatment. But it's still unclear when PCI should be performed following thrombolysis. We study when PCI should be performed following thrombolysis in this review. Conclusion: At this time, there isn't conclusive evidence about the best time to perform PCI following thrombolysis in a minimally invasive strategy, and more research is required to determine whether there is a material difference between early and late PCI after thrombolysis in terms of morbidity, mortality, and cost effectiveness. This will help standardize and improve the treatment protocol for post-thrombolysis PCI. The best time for PCI to be performed following thrombolytic therapy is not yet clear from the data, and further research is needed to establish the best time.

Keywords: PCI medical facilities, thrombolysis remains, cardiovascular disease.

Introduction

Acute coronary syndrome (ACS) continues to be a leading cause of death and accounts for many hospital admissions each year (Shafi et al., 2019). Acute coronary syndromes continue to be the primary cause of death globally despite significant advancements in diagnosis and treatment (Feigin *et al*., 2018; Vos et al., 2020). In the first six months following diagnosis, 9% to 19% of ACS patients pass away, with around half of those fatalities taking place within 30 days of the diagnosis (Sarkees et al., 2009). Ischemic heart disease causes 12% of all disability-adjusted life years lost worldwide each year (Coronado et al., 2022; khan et al., 2021). Rates of revascularization and long-term mortality following acute coronary syndromes vary substantially around the globe(Rossello *et al*., 2021; Chandrashekhar *et al*., 2020; Dagenais *et al*., 2021).

Acute ST segment elevation myocardial infarction (STEMI): non-ST segment elevation acute coronary syndrome (NSTE-ACS): and unstable angina (UA) are all included under the umbrella term "ACS" (Shafi *et al.*, 2019). For both STEMI and NSTE-ACS, effective and prompt reperfusion of the infarct-related coronary artery is essential, and percutaneous coronary intervention is an efficient way to do this (PCI) (Bagai *et al*., 2014). However, are the outcomes of early and delayed PCI significantly different? That is what this article aims to discuss.

STEMI

STEMI is declining in high-income countries (Collet *et al*., 2021): likely in part due to new patient risk profile trends, such as the decline in smoking rates in western Europe and North America, as well as the widespread use of high-sensitivity troponin (hsTn) assays to diagnose non-STEMI (NSTEMI). Nevertheless, rates of in-hospital mortality in patients with STEMI followed by shock stay high, particularly within the setting of cardiac arrest (Omer *et al*., 2020).

The most fatal form of ACS is STEMI, in which an infarct-related artery (IRA) is completely blocked, resulting in a complete cessation of coronary blood flow in the area of the blocked artery, an electrocardiogram (ECG) ST-segment elevation, and irreversible ischemia-induced myocardial necrosis within 20 to 60 minutes of onset. Patients with untreated STEMI had higher mortality and less favorable clinical outcomes than those who get a reperfusion approach (Bugiardini *et al*., 2016; Subherwal *et al*., 2012; Kadakia *et al*., 2010; Farshid *et al*., 2016; Min *et al*., 2017; Zubaid *et al*., 2017; Xavier *et al*., 2008; Mohanan *et al*., 2013).

* Corresponding author E-mail: : msremaily@yahoo.com

A quick intervention that relieves the IRA thrombotic occlusion, which reduces infarct size, preserves left ventricular function, and lowers morbidity and mortality, is the cornerstone of STEMI therapy (McKavanagh *et al*., 2018). Primary percutaneous coronary intervention (PPCI) should be used for reperfusion if the door to balloon time can be maintained within 90 minutes of a STEMI. Even for patients who must be transported to a tertiary institution, recent trials have shown that PPCI clearly outperforms pharmacologic reperfusion in terms of better event-free survival, lower incidence of intracranial hemorrhage, and unambiguous superiority (Braunwald *et al*., 2000).

Furthermore, it has been demonstrated that, when compared to a conservative approach, rescue percutaneous coronary intervention (PCI) and early routine post-thrombolysis angiography with subsequent PCI lower the rates of re-infarction and recurrent ischemia (Kolh *et al*., 2014).

NSTE-ACS

NSTE-ACS may be a more common clinical presentation than STEMI and has a poorer long-standing prognosis (Yeh *et al*., 2010; Lancellotti *et al*., 2005). The proportion of patients with NSTEMI in MI surveys increased from one-third in 1995 to more than half in 2015, mostly accounted for by a refinement within the effective diagnosis of NSTEMI (Giacobbe *et al*., 2022).

In comparison to a conservative strategy, routine early angiography and revascularization in patients with NSTE-ACS improve clinical outcomes and reduce rates of recurrent ischemia, re-hospitalization, repeat revascularization, myocardial infarction (MI): and lowered rate of death (Bavry *et al*., 2006; WHO ., 2014; Dorobantu *et al*., 2020; Damman *et al*., 2009). It has been in addition become obvious that the early intrusive method is also useful in patients with UA. The common cause of decreased myocardial perfusion in UA is coronary atherothrombosis. Lower incidence of new MI in patients who received an early intervention were linked to the ISARCOOL study (Damman *et al*., 2009). According to data from the CARESS in AMI research, high-risk patients with STEMI who receive thrombolytic therapy should be moved for PCI promptly following thrombolysis in order to maximise the effectiveness of the medication (Pels et al., 2008).

What should be done

Rapid intervention is the cornerstone of STEMI therapy and aims to relieve IRA thrombotic blockage, thereby shrinking the infarct, maintaining left ventricular function, and lowering morbidity and mortality. Fibrinolysis became the accepted technique to achieve reperfusion in the 1980s. Later, it was revealed by a number of randomised studies and meta-analyses that, once promptly attained, PPCI was linked to superior clinical outcomes to fibrinolytic therapy (McKavanagh *et al*., 2018). The mortality benefit of PPCI, however, decreases with treatment delays and diminishes when the interval between fibrinolysis and PCI passes 115 minutes (Pinto *et al*., 2006; Chakrabarti *et al*., 2012). When there will be more than 120 minutes between the first medical contact and the PCI, new recommendations advise using fibrinolytic treatment (McKavanagh *et al*., 2018). Despite these recommendations, according to data from the US National Cardiovascular Data Registry, only 51% of STEMI patients transported for PPCI were able to arrive at the first door-to-balloon time of 120 minutes (Dauerman *et al*., 2015). According to comparable European data, 65% of transferred patients experienced delays of more than 120 minutes, which were linked to higher fatality rates (Ferreira *et al*., 2022).

Numerous approaches have been developed to enhance the number of patients who can receive timely PPCI, such as prehospital STEMI diagnosis and networks that enable ambulances to transport patients directly to PCI facilities rather than the nearest hospital (McKavanagh *et al*., 2018). However, there will always be a subset of patients who are located too far from PCI facilities, and for them, fibrinolytic therapy will continue to be the preferred method of treatment (Terkelsen *et al*., 2011; Le May *et al*., 2008). The so-called pharmacoinvasive technique, which involves moving patients to a PCI facility for routine early PCI after fibrinolysis, has been shown to lower the risks of reinfarction and recurrent ischemia without increasing the risk of major bleeding. Depending on the patient's proximity to facilities, there are examples of

effective implementation of combined PPCI and pharmacoinvasive techniques in the literature (Larson *et al*., 2012): with regional systems being suggested (Henry et al., 2010).

Pharmacoinvasive strategy

Patients with STEMI who receive fibrinolysis at a non-PCI facility are treated using the pharmacoinvasive approach. Patients are moved to a PCI facility right after following fibrinolysis (without waiting for the outcome of reperfusion): and then undergo regular early PCI. Early PCI minimizes recurrent ischemia and reinfarction in patients who are successfully reperfused using fibrinolytic therapy. When a patient arrives at the PCI facility with failed reperfusion or clinical instability, they immediately undergo emergent PCI (McKavanagh *et al*., 2018).

Numerous studies also compared routine early PCI following fibrinolysis with a conservative strategy driven by ischemia or delayed PCI (Gulati *et al*., 2010; Rashid *et al*., 2016; Gersh *et al*., 2005; Di Mario *et al*., 2008; Wang *et al*., 2009). The studies found higher rates of emergency bypass surgery and higher mortality when PCI was routinely carried out within 24 hours of fibrinolysis. These studies were conducted prior to the widespread use of coronary stents and antiplatelet medications that help preserve infarct artery patency (Desch *et al*., 2010). Better results with routine early PCI after fibrinolysis were reported in studies using modern PCI procedures (including coronary stenting) and pharmacotherapy (Westerhout *et al*., 2011).

The largest such randomized trial, TRANSFER-AMI (Trial of Routine Angioplasty and Stenting After Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction): randomly assigned 1059 high-risk patients who received fibrinolytic therapy either to usual care (which include rescue PCI for failed fibrinolytic therapy) or urgent transfer to a PCI-capable facility for a routine early PCI within 6 h of fibrinolytic therapy (Cantor *et al*., 2009). In the usual care group, 17.2% of patients reached the primary endpoint, which is a composite of death, reinfarction, recurrent ischemia, new or worsening heart failure, or cardiogenic shock in 30 days, while 11.0% of patients were given an early invasive strategy (RR 0.64, 95% CI 0.47- 0.87, p = 0.004).

A meta-analysis of seven recent trials that compared a pharmacoinvasive strategy to ischemia-driven (or delayed) PCI after fibrinolytic therapy found that the pharmacoinvasive group experienced a significant decline in death or MI at 6 months to 1 year, while major bleeding or stroke rates were unaffected (Borgia *et al*., 2010).

A pharmacoinvasive method was found to be safe and effective in real-world data from a prospective registry including a rural population served by a sizable regional health network. After receiving aspirin, clopidogrel, unfractionated heparin, and half-dose fibrinolysis, 2624 consecutive patients who presented with STEMI to a hospital that was not equipped for PCI and was more than 60 miles away from the closest PCI facility were sent for PCI. Despite a longer door-to-balloon time, there was no significant differences in 30-day mortality (5.5% vs. 5.6%, p = 0.94): stroke (1.1% vs. 1.3%, P = 0.66): major bleeding (1.5% vs. 1.8%, p = 0.65): or reinfarction (1.2% vs. 2.5%, p = 0.088) when results were compared to STEMI patients presenting directly to PCI facilities for PPCI (Larson *et al*., 2012). A study of the FAST-MI found no significant difference between PPCI and a pharmacoinvasive approach in risk-adjusted mortality at 1 year (Danchin *et al*., 2008).

The STREAM trial was an international, multicenter randomised study that evaluated the effectiveness of primary PCI versus a pharmacoinvasive approach in 1892 STEMI patients who presented within three hours of the onset of symptoms but were unable to receive PPCI in less than one hour after first medical contact. [51] Death, reinfarction, shock, or congestive heart failure were the most common outcomes. The combined main endpoint between the two groups showed no statistically significant difference, with 14.3% in the primary PCI group and 12.4% in the fibrinolysis group (p = 0.21, 95% CI 0.68-1.09) (Armstrong *et al*., 2013).

The fibrinolysis group had a greater rate of intracranial bleeding (1.0% vs. 0.2%, p = 0.004). There was no significant difference in the rates of intracranial bleeding between the two groups (0.5% vs. 0.3%, p = 0.45): even after the protocol was changed to reduce the fibrinolytic dose in patients 75 years of age and older by half. The average duration from the first medical contact

to balloon inflation was 117 minutes, and nearly one-third of patients had a PPCI delay of less than 1 hour. Therefore, the outcomes of the STREAM trial could not be relevant to patients who are unable to undergo PPCI within 120 minutes of first medical contact. Current guidelines advise transfer to a PCI-capable hospital after fibrinolysis "while still hemodynamically stable and with clinical evidence of successful reperfusion," to undergo coronary angiography and revascularization within 24 hours after fibrinolysis. This recommendation is based on the findings of contemporary pharmacoinvasive trials (Class IIa, Level of Evidence B) (McKavanagh *et al*., 2018).

Timing of PCI After Fibrinolytic Therapy in STEMI

Although coronary angiography is recommended within 24 hours of fibrinolysis as part of a pharmacoinvasive strategy, the current guidelines discourage doing angiography less than 2-3 hours after fibrinolysis, in part due to the unfavourable outcomes in the facilitated PCI trials. The ideal time for angiography to be performed following fibrinolysis is still in question, though. The median time in TRANSFER-AMI, with a range of 2.5–4.2 h, was 3.2 h from registration to first balloon inflation (Cantor *et al*., 2009). When angiography was done more than 4 hours after fibrinolysis, there was a propensity to more reinfarction, according to a meta-analysis examining the timing of PCI following fibrinolysis (Madan *et al*., 2015).

Timing of coronary angiography in NSTE-ACS

Aspirin loading therapy and systemic anticoagulation are part of the immediate treatment for NSTE-ACS patients (Collet *et al*., 2021). The best time to do an angiography in NSTE-ACS is still under debate. The primary determining factor for timing is clinical risk stratification, with very high-risk patients (e.g., hemodynamic instability, refractory chest pain, life-threatening arrhythmia) necessitating emergent (<2 h) angiography, high-risk patients (e.g.; Global Registry of Acute Coronary Events [GRACE] score >140) undergoing angiography within 24 h, and low-risk patients being subjected to a selective invasive strategy (Collet *et al*., 2021).

Growing evidence has confirmed the necessity of early angiography in high-risk patients and strongly supports the safety of late angiography in low-risk patients, such as in the VERDICT trial (Kofoed *et al*., 2018). The routine use of a P2Y12 inhibitor prior to angiography in patients with NSTE-ACS and a planned early invasive strategy is no longer recommended (Omer *et al*., 2020). Coronary computed tomography angiography (CCTA) may be used to expand non-invasive anatomical evaluation in the future (Abdelrahman *et al*., 2020; Edelberg *et al*., 2022; Gray *et al*., 2016; Linde *et al*., 2020).

Conclusion

Based on anticipated first medical contact to balloon durations, regional STEMI networks should deliver both primary PCI and pharmacoinvasive strategy. Just after receiving fibrinolytic therapy, patients should be sent to PCI facilities in order to undergo coronary angiography and revascularization. Data on when PCI should be performed after thrombolytic therapy, however, are inconclusive, and further research is needed to determine the most appropriate timing.

References

Abdelrahman, K. M.; Chen, M. Y.; Dey, A. K.; Virmani, R.; Finn, A. V.; Khamis, R. Y.; ... & Mehta, N. N. (2020). Coronary computed tomography angiography from clinical uses to emerging technologies: JACC state-of-the-art review. *Journal of the American College of Cardiology*, 76(10): 1226-1243.

Armstrong, P. W.; Gershlick, A. H. & Van de Werf, F. (2013). Fibrinolysis or primary PCI in myocardial infarction. The New England journal of medicine, 369(3): 280-1.

Bagai, A.; Dangas, G. D.; Stone, G. W.; & Granger, C. B. (2014). Reperfusion strategies in acute coronary syndromes. Circulation Research, 114(12): 1918-1928.

Bavry, A. A.; Kumbhani, D. J.; Rassi, A. N.; Bhatt, D. L.; & Askari, A. T. (2006). Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomized clinical trials. Journal of the American College of Cardiology, 48(7): 1319-1325.

Borgia F, Goodman SG, Halvorsen S, et al. (2010). Early routine percutaneous coronary intervention after fibrinolysis vs. standard therapy in ST segment elevation myocardial infarction: a meta-analysis. Eur Heart J. 31:2156–6973.

Braunwald, E.; Antman, E. M.; Beasley, J. W.; Califf, R. M.; Cheitlin, M. D.; Hochman, J. S.; ... & Smith, S. C. (2000). ACC/AHA guidelines for the management of patients with unstable angina and non–ST-segment elevation myocardial infarction: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). *Journal of the American College of Cardiology*, 36(3): 970-1062.

Bugiardini, R.; & Badimon, L. (2016). The International Survey of Acute Coronary Syndromes in Transitional Countries (ISACS-TC): 2010–2015. *International Journal of Cardiology*, *217*, S1-S6.

Cantor, W. J.; Fitchett, D.; Borgundvaag, B.; Ducas, J.; Heffernan, M.; Cohen, E. A.; ... & Goodman, S. G. (2009). Routine early angioplasty after fibrinolysis for acute myocardial infarction. *New England Journal of Medicine*, 360(26): 2705-2718.

Chakrabarti, A. K.; Gibson, C. M.; & Pinto, D. S. (2012). Optimal selection of STEMI treatment strategies in the current era: benefit of transferring STEMI patients for PCI compared with administration of onsite fibrinolytic therapy. *Current Opinion in Cardiology*, *27*(6): 651-654.

Chandrashekhar, Y.; Alexander, T.; Mullasari, A.; Kumbhani, D. J.; Alam, S.; Alexanderson, E.; & Narula, J. (2020). Resource and infrastructure-appropriate management of ST-segment elevation myocardial infarction in low - and middle- income countries. *Circulation*, 141 (24): 2004-2025.

Collet, J. P.; Thiele, H.; Giannitsis, E.; Sibbing, D.; Barthélémy, O.; Bauersachs, J.; ... & Crea, F. (2021). Debate: prasugrel rather than ticagrelor is the preferred treatment for NSTE-ACS patients who proceed to PCI and pretreatment should not be performed in patients planned for an early invasive strategy. *European Heart Journal*, 42: 1289–367.

Coronado, F. (2022). Global Responses to Prevent, Manage, and Control Cardiovascular Diseases. *Preventing Chronic Disease*, 19.

Dagenais, G. R.; Leong, D. P.; Rangarajan, S.; Lanas, F.; Lopez-Jaramillo, P.; Gupta, R.; ... & Yusuf, S. (2020). Variations in common diseases, hospital admissions, and deaths in middle-aged adults in 21 countries from five continents (PURE): a prospective cohort study. The Lancet, 395(10226): 785-794.

Damman, P.; Tijssen, J.; & de Winter, R. (2009). Acute coronary syndromes. *The New England journal of medicine*, *361*(9): 925-27

Danchin, N.; Coste, P.; Ferrières, J.; Steg, P. G.; Cottin, Y.; Blanchard, D.; ... & Simon, T. (2008). Comparison of thrombolysis followed by broad use of percutaneous coronary intervention with primary percutaneous coronary intervention for ST-segment–elevation acute myocardial infarction: data from the French Registry on Acute ST-Elevation Myocardial Infarction (FAST-MI). *Circulation*, 118(3): 268-276.

Dauerman, H. L.; Bates, E. R.; Kontos, M. C.; Li, S.; Garvey, J. L.; Henry, T. D.; ... & Roe, M. T. (2015). Nationwide Analysis of Patients With ST-Segment–Elevation Myocardial Infarction Transferred for Primary Percutaneous Intervention: Findings From the American Heart Association Mission: Lifeline Program. *Circulation: Cardiovascular Interventions*, 8(5): e002450.

Desch, S.; Eitel, I.; Rahimi, K.; de Waha, S.; Schuler, G.; & Thiele, H. (2010). Timing of invasive treatment after fibrinolysis in ST elevation myocardial infarction–a meta-analysis of immediate or early routine versus deferred or ischemia-guided randomised controlled trials. *Heart*, 96(21): 1695-1702.

Di Mario, C.; Dudek, D.; Piscione, F.; Mielecki, W.; Savonitto, S.; Murena, E.; ... & CARESS-in-AMI (Combined Abciximab RE-teplase Stent Study in Acute Myocardial Infarction) Investigators. (2008). Immediate angioplasty versus standard therapy with rescue angioplasty after thrombolysis in the Combined Abciximab REteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI): an open, prospective, randomised,

multicentre trial. *The Lancet*, 371(9612): 559-568.

Dorobantu, M.; Edvardsen, T.; Folliguet, T.; Gale, C. P.; Gilard, M.; Jobs, A.; & Jüni, P. (2016). Corrigendum to: Multimodality Imaging in Valvular Heart Disease Eur Heart J 2020; doi: 10.1093/eurheartj/ehaa768 In the originally published version of this manuscript, several errors regarding the placement of the following figures were noted: Take-home figure, Figure 1.; Figure 2.; Figure 3.; Figure 4. and Figure 5. This error has now been corrected. *ESC*, 37: 267-315.

Edelberg, J. M.; Sehnert, A. J.; Mealiffe, M. E.; Del Rio, C. L.; & McDowell, R. (2022). The Impact of Mavacamten on the Pathophysiology of Hypertrophic Cardiomyopathy: A Narrative Review. *American Journal of Cardiovascular Drugs*, 1-14.

Farshid, A.; Brieger, D.; Hyun, K.; Hammett, C.; Ellis, C.; Rankin, J.; ... & French, J. (2016). Characteristics and clinical course of STEMI patients who received no reperfusion in the Australia and New Zealand SNAPSHOT ACS registry. *Heart, Lung and Circulation*, 25(2): 132-139.

Feigin, V.; & GBD 2017 Causes of Death Collaborators. (2018). Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*, 392(10159): 1736-1788.

Ferreira, D. (2022). If "Time Is Muscle," Then the Patient's Knowledge Must Save Time. *Arquivos Brasileiros de Cardiologia*, *119*, 35-36.

Gersh, B. J.; Stone, G. W.; White, H. D.; & Holmes, D. R. (2005). Pharmacological facilitation of primary percutaneous coronary intervention for acute myocardial infarction: is the slope of the curve the shape of the future?. *Jama*, 293(8): 979-986.

Giacobbe, F.; Macaya, F.; & Cerrato, E. (2022). DISCO study suggests that less is more regarding antiplatelet therapy in spontaneous coronary artery dissection. *European Heart Journal*.

Gray, A. J.; Roobottom, C.; Smith, J. E.; Goodacre, S.; Oatey, K.; O'brien, R.; ... & Newby, D. E. (2016). The RAPID-CTCA trial (Rapid Assessment of Potential Ischaemic Heart Disease with CTCA)—a multicentre parallel-group randomised trial to compare early computerised tomography coronary angiography versus standard care in patients presenting with suspected or confirmed acute coronary syndrome: study protocol for a randomised controlled trial. *Trials*, 17(1): 1-13.

Gulati, R.; & Gersh, B. J. (2010). Utilization of Facilitated and Rescue Angioplasty. In *Clinical Guide to Primary Angioplasty* (pp. 159-168). CRC Press.

Henry, T. D.; Gibson, C. M.; & Pinto, D. S. (2010). Moving toward improved care for the patient with ST-elevation myocardial infarction: a mandate for systems of care. *Circulation: Cardiovascular Quality and Outcomes*, 3(5): 441-443.

Kadakia, M. B.; Desai, N. R.; Alexander, K. P.; Chen, A. Y.; Foody, J. M.; Cannon, C. P.; ... & National Cardiovascular Data Registry. (2010). Use of anticoagulant agents and risk of bleeding among patients admitted with myocardial infarction: a report from the NCDR ACTION Registry–GWTG (National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With the Guidelines). *JACC: Cardiovascular Interventions*, 3(11): 1166-1177.

Khan, S.; & Hsu, C. H. (2021). The who, where, and when of REBOA for refractory out-of-hospital cardiac arrest. *Resuscitation*, 165, 179-181.

Kofoed, K. F.; Kelbæk, H.; Hansen, P. R.; Torp-Pedersen, C.; Høfsten, D.; Kløvgaard, L.; ... & Engstrøm, T. (2018). Early versus standard care invasive examination and treatment of patients with non-ST-segment elevation acute coronary syndrome: VERDICT randomized controlled trial. *Circulation*, 138(24): 2741-2750.

Kolh, P.; & Windecker, S. (2014). ESC/EACTS myocardial revascularization guidelines 2014. *European heart journal*, 35(46): 3235-3236.

Lancellotti, P.; Gérard, P. L.; & Piérard, L. A. (2005). Long-term outcome of patients with heart failure and dynamic functional mitral

regurgitation. *European heart journal*, 26(15): 1528-1532.

Larson, D. M.; Duval, S.; Sharkey, S. W.; Garberich, R. F.; Madison, J. D.; Stokman, P. J.; ... & Henry, T. D. (2012). Safety and efficacy of a pharmaco-invasive reperfusion strategy in rural ST-elevation myocardial infarction patients with expected delays due to long-distance transfers. *European heart journal*, 33(10): 1232-1240.

Larson, D. M.; Duval, S.; Sharkey, S. W.; Garberich, R. F.; Madison, J. D.; Stokman, P. J.; ... & Henry, T. D. (2012). Safety and efficacy of a pharmaco-invasive reperfusion strategy in rural ST-elevation myocardial infarction patients with expected delays due to long-distance transfers. *European heart journal*, 33(10): 1232-1240.

Le May, M. R.; So, D. Y.; Dionne, R.; Glover, C. A.; Froeschl, M. P.; Wells, G. A.; ... & Labinaz, M. (2008). A citywide protocol for primary PCI in ST-segment elevation myocardial infarction. *New England Journal of Medicine*, 358(3): 231-240.

Linde, J. J.; Kelbaek, H.; Hansen, T. F.; Sigvardsen, P. E.; Torp-Pedersen, C.; Bech, J.; ... & Kofoed, K. F. (2020). Coronary CT angiography in patients with non-ST-segment elevation acute coronary syndrome. *Journal of the American College of Cardiology*, 75(5): 453-463.

Madan, M.; Halvorsen, S.; Di Mario, C.; Tan, M.; Westerhout, C. M.; Cantor, W. J.; ... & Goodman, S. G. (2015). Relationship between time to invasive assessment and clinical outcomes of patients undergoing an early invasive strategy after fibrinolysis for ST-segment elevation myocardial infarction: a patient-level analysis of the randomized early routine invasive clinical trials. *JACC: Cardiovascular Interventions*, 8(1 Part B): 166-174.

McKavanagh, P.; Zawadowski, G.; Cantor, W.J. et al. (2018). Utilization of PCI After Fibrinolysis In Primary Angioplasty. Springer, Singapore, 53-67

Min, H. K.; Park, J. Y.; Choi, J. W.; Ryu, S. K.; Kim, S.; Song, C. S.; ... & Kim, Y. B. (2017). Long-term clinical outcome of acute myocardial infarction according to the early revascularization method: a comparison of primary percutaneous coronary interventions and fibrinolysis followed by routine invasive treatment. *Journal of Yeungnam Medical Science*, 34(2): 191-199.

Mohanan, P. P.; Mathew, R.; Harikrishnan, S.; Krishnan, M. N.; Zachariah, G.; Joseph, J.; & Kerala ACS Registry Investigators. (2013). Presentation, management, and outcomes of 25 748 acute coronary syndrome admissions in Kerala, India: results from the Kerala ACS Registry. *European heart journal*, 34(2): 121-129.

Omer, M. A.; Tyler, J. M.; Henry, T. D.; Garberich, R.; Sharkey, S. W.; Schmidt, C. W.; ... & Garcia, S. (2020). Clinical characteristics and outcomes of STEMI patients with cardiogenic shock and cardiac arrest. *Cardiovascular Interventions*, 13(10): 1211-1219.

Pels, K.; Schröder, J.; Witzenbichler, B.; Müller, D.; Morguet, A.; Pauschinger, M.; ... & Arntz, H. R. (2008). Prehospital versus periprocedural abciximab in ST-elevation myocardial infarction treated by percutaneous coronary intervention. *European Journal of Emergency Medicine*, 15(6): 324-329.

Pinto, D. S.; Kirtane, A. J.; Nallamothu, B. K.; Murphy, S. A.; Cohen, D. J.; Laham, R. J.; ... & Gibson, C. M. (2006). Hospital delays in reperfusion for ST-elevation myocardial infarction: implications when selecting a reperfusion strategy. *Circulation*, 114(19): 2019-2025.

Rashid, M. K.; Guron, N.; Bernick, J.; Wells, G. A.; Blondeau, M.; Chong, A. Y.; ... & Le May, M. R. (2016). Safety and efficacy of a pharmacoinvasive strategy in ST-segment elevation myocardial infarction: a patient population study comparing a pharmacoinvasive strategy with a primary percutaneous coronary intervention strategy within a regional system. *Cardiovascular Interventions*, 9(19): 2014-2020.

Rossello, X.; Ramis-Barceló, M. F.; & Raposeiras-Roubín, S. (2021). Acute myocardial infarction with high Killip class: do geographic differences matter?. *European Heart Journal. Acute Cardiovascular Care*, 74: 1454–61.

Sarkees, M. L.; & Bavry, A. A. (2009). Acute coronary syndrome (unstable angina and non-

ST elevation MI). *BMJ clinical evidence*, 2009.

Shafi, M. J.; & Nasrin, S. (2019). Outcome of Early vs. Delayed Invasive Intervention in Acute Coronary Syndrome Patients Attending a Selected Specialized Hospital: A Comparative Study. *Cardiovascular Journal*, 11(2): 129-138.

Subherwal, S.; Peterson, E. D.; Dai, D.; Thomas, L.; Messenger, J. C.; Xian, Y.; & Rao, S. V. (2012). Temporal trends in and factors associated with bleeding complications among patients undergoing percutaneous coronary intervention: a report from the National Cardiovascular Data CathPCI Registry. *Journal of the American College of Cardiology*, 59(21): 1861-1869.

Terkelsen, C. J.; Jensen, L. O.; Tilsted, H. H.; Thaysen, P.; Ravkilde, J.; Johnsen, S. P.; ... & Lassen, J. F. (2011). Primary percutaneous coronary intervention as a national reperfusion strategy in patients with ST-segment elevation myocardial infarction. *Circulation: cardiovascular interventions*, 4(6): 570-576.

Vos, T.; Lim, S. S.; Abbafati, C.; Abbas, K. M.; Abbasi, M.; Abbasifard, M.; & Bhutta, Z. A. (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet*, 396(10258): 1204-1222.

Wang, H.; Escobar, J. M.; & Denktas, A. E. (2009). Prehospital fibrinolytic therapy for ST-elevation acute myocardial infarction. *Current Cardiovascular Risk Reports*, *3*(5): 339-344.

Westerhout, C. M.; Bonnefoy, E.; Welsh, R. C.; Steg, P. G.; Boutitie, F.; & Armstrong, P. W. (2011). The influence of time from symptom onset and reperfusion strategy on 1-year survival in ST-elevation myocardial infarction: a pooled analysis of an early fibrinolytic strategy versus primary percutaneous coronary intervention from CAPTIM and WEST. *American heart journal*, 161(2): 283-290.

WHO Expert Committee on the Selection, Use of Essential Medicines, & World Health Organization. (2014). *The Selection and Use of Essential Medicines: Report of the WHO Expert Committee, 2013 (including the 18th WHO Model List of Essential Medicines and the 4th WHO Model List of Essential Medicines for Children)* (Vol. 985). World Health Organization.

Xavier, D. (2008). pais p, Devereaux pJ, et al. Create registry investigators. treatment and outcomes of acute coronary syndromes in India (Create). a prospective analysis of registry data. *Lancet*, 371: 1435-42.

Yeh, R. W.; Sidney, S.; Chandra, M.; Sorel, M.; Selby, J. V.; & Go, A. S. (2010). Population trends in the incidence and outcomes of acute myocardial infarction. *New England Journal of Medicine*, 362(23): 2155-2165.

Zubaid, M.; Rashed, W.; Alsheikh-Ali, A. A.; Garadah, T.; Alrawahi, N.; Ridha, M.; ... & Amin, H. (2017). Disparity in ST-segment elevation myocardial infarction practices and outcomes in Arabian Gulf countries (Gulf COAST registry). *Heart Views: the Official Journal of the Gulf Heart Association*, 18(2): 41.