Original Research Article

Outcome of Primary Angioplasty as Compared with Thrombolytic Therapy for Acute Myocardial Infarction

ABSTRACT

Background:*Acute myocardial infarction (AMI), commonly known as a heart attack, occurs due to reduced or blocked blood flow in the heart's coronary artery, leading to damage to the heart muscle. Prompt medical intervention is crucial to restore blood circulation and improve patient outcomes. In recent years, advancements in treating AMI have significantly improved prognoses, with intravenous thrombolytic therapy showing a 20% to 30% reduction in early mortality rates. Two primary reperfusion therapies used are primary angioplasty and thrombolytic therapy. Primary angioplasty involves mechanically opening the blocked artery, while thrombolytic therapy uses drugs to dissolve blood clots.*

Aim of the study: *This study aims to compare the outcomes of these two interventions to enhance our understanding of their effectiveness and safety.*

Methods:*This retrospective compressional study was conducted at the Department of Cardiology, Apollo Imperial Hospital, Chittagong, Bangladesh. It analyzed 480 consecutive patients who underwent Coronary Angiography (CA), with or without Percutaneous Coronary Intervention (PCI). The study spanned one year, from January 2021 to December 2022.*

Result:*This study involved the analysis of 98 patients divided into two groups. The age distribution revealed that most patients were in the 51-60 age group, with a higher number of males (65%) than females (35%). The baseline characteristics of both groups were compared, showing no significant difference in individuals with anterior infarction. However, a highly significant difference was observed in the presence of a patent infarct-related vessel, with Group A having 89.58% and Group B having 66% of individuals with this characteristic.The study also investigated mortality and causes of death within 30 days of treatment. Group B exhibited a significantly higher proportion of cardiac-related deaths (6%) than Group A (2.08%). Additionally, heart failure was more prevalent in Group B (6%) than in Group A (2.08%).Regarding interventions, "Early Angioplasty" was administered to significantly more patients in Group B (34%) compared to Group A (4.17%). However, "Coronary-artery bypass grafting" did not show a significant difference in treatment outcomes between the group'sLate interventions ("Late Angioplasty" and "Coronary-artery") also did not yield significant differences in outcomes between the two groups.The usage of medications at the end of follow-up revealed that Warfarin and Nitrates showed statistically significant differences between the groups, while other medications did not display significant variations.Overall, this study highlighted notable differences in mortality and treatment outcomes between the two groups, particularly concerning cardiac-related deaths and the presence of a patent infarct-related vessel.*

Conclusion:*Recent studies have shown that primary angioplasty outperforms thrombolytic therapy in managing acute myocardial infarction, improving patient outcomes and lowering mortality rates. Consequently, healthcare professionals are strongly encouraged to prioritize primary angioplasty as the first-line treatment for acute myocardial infarction, as it can enhance patient outcomes and alleviate the impact of cardiovascular diseases.*

Keywords: *Primary Angioplasty, Thrombolytic Therapy and Acute Myocardial Infarction.*

INTRODUCTION

Acute myocardial infarction (AMI), colloquially referred to as a heart attack, ensues when there is a reduction or cessation of blood flow in the heart's coronary artery, resulting in myocardial damage. This life-threatening condition necessitates prompt medical intervention to reinstate blood circulation to the impacted cardiac region[1]. In recent years, advancements in treating acute myocardial infarction (AMI) have improved patient prognoses, primarily through the prompt restoration of blood flow in the infarct-related coronary artery. Studies have demonstrated that intravenous thrombolytic therapy significantly reduces the early mortality rate by approximately 20% to 30%[2-4].Over the years, significant advancements have been made in treating AMI, particularly in the reperfusion strategies employed to restore blood flow and minimize myocardial damage quickly. Two primary reperfusion therapies widely used are primary angioplasty (percutaneous coronary intervention or PCI) and thrombolytic therapy (also known as fibrinolytic). Primary angioplasty involves the mechanical opening of the

blocked coronary artery using a balloon catheter, often followed by the placement of a stent to maintain arterial patency. In contrast, thrombolytic therapy entails the meticulous administration of pharmacological agents designed to efficaciously dissolve the intracoronary blood clot, reinstating unimpeded blood flow to the ischemic myocardium. Simultaneously, these therapeutic modalities endeavour to salvage the imperilled cardiac musculature, thus fostering myocardial preservation and recovery.Notable trials include the DANAMI-2 (DANish trial in Acute Myocardial Infarction 2), which demonstrated the superiority of primary angioplasty over thrombolytic therapy in reducing mortality and reinfarction rates. In alignment with extant literature, notable investigations, including the CAPTIM (Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction) trial, have substantiated akin outcomes when evaluating the efficacy of primary angioplasty against thrombolytic therapy in the context of acute myocardial infarction[5,6].A comprehensive meta-analysis integrating data from ten meticulously conducted randomized trials has compellingly affirmed that in the initial weeks following an acute myocardial infarction, primary angioplasty consistently exhibits significantly reduced mortality rates, nonfatal reinfarction, and stroke compared to thrombolytic therapy[7]. In addition to clinical trials, observational studies have also provided valuable insights into the comparative effectiveness of these interventions. The GRACE (Global Registry of Acute Coronary Events) registry, which included a large cohort of AMI patients, found that primary angioplasty was associated with lower mortality rates than thrombolytic therapy. This study aims to compare the outcomes of primary angioplasty with thrombolytic therapy for AMI, shedding light on the release interventions effectiveness and safety of the randomized controlled trials and meta-analyses have contributed to our understanding of the outcomes associated with these reperfusion strategies.

METHODOLOGY & MATERIALS

This retrospective compressional study was conducted at the Department of Cardiology, Apollo Imperial Hospital, Chittagong, Bangladesh. It analyzed 480 consecutive patients who underwent Coronary Angiography (CA), with or without Percutaneous Coronary Intervention (PCI). The study spanned one year, from January 2021 to December 2022.This study aims to examine and compare the long-term advantages of primary angioplasty and thrombolytic therapy in individuals diagnosed with acute myocardial infarction (AMI). The research entails a retrospective analysis of medical records and data from AMI patients who received either primary angioplasty or thrombolytic therapy. Ninety-eight patients were enrolled in the study and categorized into two groups. After obtaining informed consent, the patients were subjected to a randomized allocation, with one group undergoing primary coronary angioplasty while the other received streptokinase treatment. Both groups were administered aspirin and heparin as part of the treatment protocol. Those allocated to the streptokinase group were intravenously administered 1.5 million units of the medication over one hour.On the other hand, patients assigned to the angioplasty group were expeditiously transferred to the catheterization laboratory, where the procedure was promptly performed, provided their coronary anatomy was deemed suitable, using standard and established techniques.The patient population was divided into two groups: the Angioplasty group, consisting of 48 patients, and the Streptokinase group, consisting of 50 patients.

- **Group A:**Angioplasty group
- **Group B:** Streptokinase group

- **Inclusion criteria:**
  - Individuals without any contraindications to thrombolytic intervention were included as patients.
  - Patients with acute myocardial infarction symptoms lasting over 30 minutes were considered.
  - Patients requiring an electrocardiogram showing ST-segment elevation of 1 mm (0.1 mV) or more in two or more adjacent leads were included.
  - Patients demonstrating ongoing ischemia within 6 to 24 hours after the onset of symptoms were eligible.

- **Exclusion criteria:**
  - Patients who aged less than 40 years.
  - Pregnant patients.
  - Patients who did not meet our criteria.
  - Patients who were lost to follow-up.

The clinical description of the patients and the study's preliminary findings have been previously recorded. Nearly all patients who arrived at our hospital with ST-segment elevation accompanying acute myocardial infarction agreed

to participate, resulting in a comprehensive and representative group for our study. We evaluated the outcomes of death and the combined occurrence of death and nonfatal reinfection. All outcomes were analyzed based on the intention-to-treat principle. Student's t-test were used to assess differences between the means of the groups. Proportional differences were tested using chi-square analysis. Statistical significance was determined by a two-tailed P value of less than 0.05. We calculated relative risks along with 95% confidence intervals.

RESULT

In this study, we enrolled and analyzed 98 patients into two groups. Table 1 shows the age distribution of the study population, where the most, 44.90% of patients were from the age group 51-60 years, 2nd most, 35.71% of patients, were from the age range 41-50 years, and 19.39% of patients were aged between 61-70 years. 65% of patients were male, and the rest of the 35% of patients were females (Figure 1). Table 2 presents the baseline Characteristics of Patients Assigned to both groups. In both groups, 19 individuals had anterior infarction with different percentages, and the p-value is o.6, which shows non-significance between the two groups. The "Patent infarct-related vessel" characteristic is represented by 43 individuals in Group A (89.58%) and 33 individuals in Group B (66%). The P-value is less than 0.001, signifying a highly significant difference between the two groups concerning the presence of a patent infarct-related vessel. Table 2 shows the mortality and causes of early and late death (≤30 days after study treatment); the most significant finding was related to cardiac-related deaths, which accounted for a higher proportion in Group B (6%) compared to Group A (2.08%). This difference was statistically significant, with a p-value of less than 0.01. Another notable observation was heart failure, which was also more prevalent in Group B (6%) compared to Group A (2.08%). Similarly, this difference was statistically significant with a p-value of less than 0.01 (Table 3). Table 4 shows that cardiac-related deaths were notably higher in Group B, with 14% of individuals succumbing to cardiac issues compared to only 6.25% in Group A (P-value < 0.01). Specifically, sudden death also showed a significant difference, with 8% of Group B experiencing it as opposed to 2.08% in Group A (P-value = 0.02). While other causes of death did not exhibit statistically significant differences between the two groups (P-values > 0.05), it is important to note that the occurrence of stroke was more prominent in Group A (2.08%) compared to Group B (0%), and the incidence of lung cancer was marginally higher in Group B (2%) than in Group A (2.08%). The intervention "Early (≤30 days) Angioplasty," was administered to 2(4.17%) patients in Group A, while 17(34.00%) patients in Group B received the same treatment. The P-value for this comparison was <0.001, indicating a highly significant difference between the two groups. In contrast, for "Coronary-artery bypass grafting," 4 patients in each group underwent the same procedure. The P-value for this comparison was 0.77, suggesting no significant difference between the treatment outcomes in Group A and Group B. Moreover, the researchers also analyzed the effects of "Late (>30 days) Angioplasty" and "Coronary-artery" interventions. In the case of "Late (>30 days) Angioplasty," 10(20.83%) patients in Group A received the treatment, while 8(16%) patients in Group B received the same intervention. The P-value for this comparison was 0.31, indicating no significant difference in outcomes between the two groups. Lastly, for the "Coronary-artery" treatment, 6 patients in Group A underwent the procedure, making up 12.50% of the group, while 23 patients in Group B received the treatment, representing 12%. The P-value for this comparison was 0.92, implying no significant difference in treatment outcomes between the two groups (Table 5). The use of medications at the end of follow-up is shown in Table 6, where one of the major findings was related to the usage of Warfarin. In Group A, 5 participants (20.83%) received Warfarin, while in Group B, the number increased to 10 participants (20%). This difference was statistically significant, with a P-value of 0.02. Another noteworthy result was observed with the administration of Nitrates. In Group A, 7 participants (27.08%) received Nitrates; in Group B, the number was slightly higher at 13 participants (26%). This difference also showed statistical significance, with a P-value of 0.01. On the other hand, medications like Aspirin, Beta-blockers, Calcium-channel blockers, Digitalis, Diuretics, and Angiotensin-converting-enzyme inhibitors did not display statistically significant differences in usage between the two groups (P-values > 0.05).

Table 1: Age distribution of the study population (N=98).

Age range (Years)	Frequency	Percentage
41-50	35	35.71
51-60	44	44.90
61-70	19	19.39

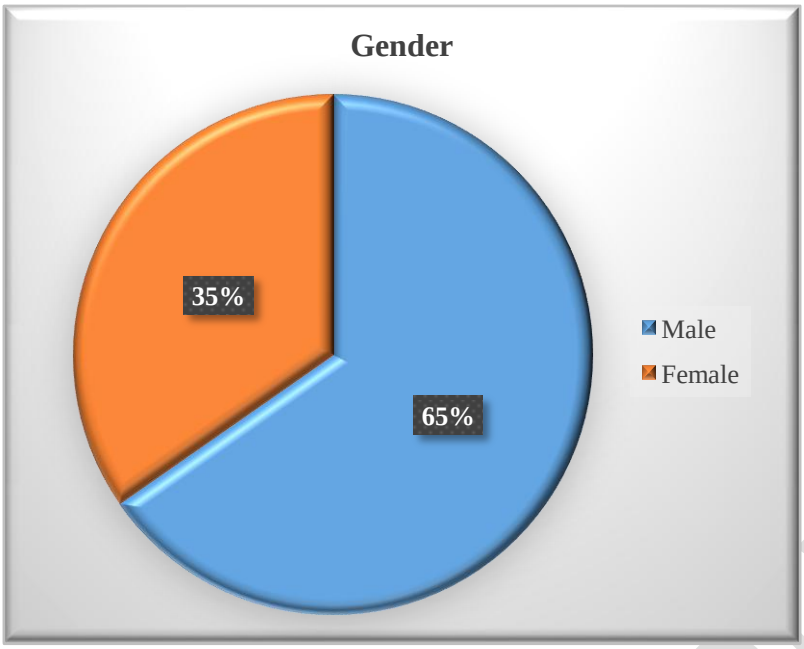

Figure 1: Gender distribution of the study population (N=98).

Table 2: Base-Line Characteristics of Patients Assigned both groups.

Characteristics	Group A (N=48)		Group B (N=50)		P-value
	N	%	N	%	
Anterior infarction	19	39.58	19	38	0.6
Previous infarction	9	18.75	7	14	0.29
Diabetes	4	8.33	0	0	1
Patent infarct-related vessel	43	89.58	33	66	<0.001
Left ventricular ejection fraction	7	14.58	0	0	0.006

Table 3: Mortality and Causes of Early and Late Death (≤30 days after study treatment).

Cause of death	Group A (N=48)		Group B (N=50)		P-value
	N	%	N	%	
Cardiac	1	2.08	3	6	<0.01
Myocardial rupture	1	2.08	1	2	1
Heart failure	1	2.08	3	6	<0.01
Sudden death	0	0.00	1	2	1
Noncardiac	0	0.00	1	2	1
Stroke	0	0.00	1	2	1
Lung cancer	0	0.00	0	0	1
Other cancer	0	0.00	0	0	1
Other	0	0.00	0	0	1

Table 4: Mortality and Causes of Early and Late Death (>30 days after study treatment).

Cause of death	Group A (N=48)		Group B (N=50)		P-value
	N	%	N	%	
Cardiac	3	6.25	7	14	<0.01
Myocardial rupture	0	0.00	1	2	0.49
Heart failure	1	2.08	2	4	0.25
Sudden death	1	2.08	4	8	0.02
Noncardiac	3	6.25	2	4	0.19
Stroke	1	2.08	0	0	0.5

Lung cancer	1	2.08	1	2	1
Other cancer	1	2.08	1	2	0.72
Other	1	2.08	1	2	1

Table 5: Need for Additional Revascularization Procedures.

Time	Group A (N=48)		Group B (N=50)		P-value
	N	%	N	%	
Early (<30 days) Angioplasty	2	4.17	17	34.00	<0.001
Coronary-artery bypass grafting	4	8.33	4	8.00	0.77
Late (>30 days) Angioplasty	10	20.83	8	16.00	0.31
Coronary-artery	6	12.50	6	12.00	0.92

Table 6: Use of Medications at the End of Follow-Up.

Medication	Group A (N=48)		Group B (N=50)		P-value
	N	%	N	%	
Aspirin	43	89.58	43	86	0.4
Warfarin	5	20.83	10	20	0.02
Statins	20	43.75	21	42	0.91
Beta-blockers	19	45.83	22	44	0.4
Calcium-channel blockers	11	18.75	9	18	0.4
Nitrates	7	27.08	13	26	0.01
Digitalis	2	8.33	4	8	0.38
Diuretics	7	25.00	12	24	0.03
Angiotensin-converting-enzyme inhibitors	15	39.58	19	38	0.29
Antiarrhythmic drugs	1	2.08	1	2	0.71

DISCUSSION

In this study, the comparison between primary angioplasty and intravenous streptokinase therapy reveals that primary angioplasty results in reduced mortality and reinfarction rates during the initial 30-day period. The risk of cardiac death is strongly associated with left ventricular ejection fraction and initial and permanent patency of infarct-related coronary arteries. Moreover, there is a correlation between readmission for heart failure and the usage of medications that are connected to impaired left ventricular function. Despite primary angioplasty initially incurring higher costs than thrombolytic therapy, its long-term follow-up demonstrates comparatively lower charges primarily due to a substantial reduction in hospital readmissions for ischemia. The main goal of all reperfusion therapies is to swiftly and fully restore blood flow in blocked coronary arteries, a principle that has been confirmed through the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries trial [8]. Preserving the openness of the coronary arteries, which involves restoring regular blood flow in the vessel affected by the infarction, safeguards myocardial tissue and enhances survival rates. Primary angioplasty results in superior patency rates compared to thrombolytic agents [8-12]. The data obtained from this study indicates that patients undergoing angioplasty, as opposed to those receiving streptokinase, experience a higher patency rate. This, in turn, leads to a higher left ventricular ejection fraction, a reduced incidence of reinfarction, and improved survival. This indicates that utilizing thrombolytic agents or supplementary therapies that result in increased rates of early and consistent TIMI grade 3 flow may provide comparable advantages. Successful primary angioplasty has the potential to improve long-term clinical outcomes by lowering the incidence of re-occlusion of the infarct-related artery to below 10%, as opposed to re-occlusion rates of up to 30% following successful thrombolytic reperfusion [13]. Reinfarctions, particularly within the first year after the acute coronary event, tend to be linked to the artery originally occluded and associated with the previous infarction. This supports the notion that coronary angioplasty possesses a plaque-sealing effect [14]. The inclusion of left ventricular ejection fraction as a primary outcome measure in acute myocardial infarction trials has sparked debates and controversies [15,16]. Certain studies indicate that prompt reperfusion may restrict the size of the infarction and enhance the function of the left ventricle, consequently leading to improved long-term survival rates [8,17,18]. The findings of this study validate that increased rates of early and sustained patency of the infarct-related vessel correlate with enhanced left ventricular

function. This improvement is likely attributed, at least in part, to the impact of successful reperfusion on left ventricular remodeling [19]. Heart failure is a prevailing reason for hospitalization and mortality, with its incidence on the rise. A recent study reveals that myocardial infarction significantly elevates the risk of developing left ventricular dysfunction and, subsequently, heart failure [20]. In this specific context, the discovery that the admission rate for heart failure was significantly lower in the angioplasty group compared to the streptokinase group carries crucial clinical importance. Moreover, the dissimilarities in medication utilization and functional status observed at the end of the follow-up, favoring the angioplasty group, indicate that the elevated left ventricular ejection fraction in the angioplasty group prior to the initial hospital discharge played a crucial role in safeguarding long-term ventricular function. The higher utilization of warfarin and diuretics within the streptokinase group might be associated with the diminished left ventricular function in this particular group. Diuretics are commonly employed to address heart failure, while warfarin is used for cases of severely depressed ventricular function or aneurysms. Angina is commonly associated with the utilization of nitrates in everyday situations. Given the substantial number of patients admitted to hospitals for heart failure treatment, ischemic events, or additional revascularization procedures, it appears that the utilization of beta-blockers and angiotensin-converting enzyme inhibitors for optimal secondary prevention in both groups may be inadequate [21]. Attaining the best possible prevention of a second myocardial infarction appears to be a formidable task in the realm of general practice. Despite the increasing prevalence of these drugs, numerous opportunities to prevent reinfarction after an initial infarction are still being overlooked [22, 23].

Limitations of the study:One limitation of the study could be the retrospective nature of the data, which may introduce potential biases and confounding factors. Additionally, the study's scope might not account for all variations in patient demographics, medical histories, and treatment protocols, leading to limited generalizability of the findings. Furthermore, the long-term outcomes and follow-up data may be lacking, hindering a comprehensive assessment of the sustained effectiveness of primary angioplasty compared to thrombolytic therapy for acute myocardial infarction.

CONCLUSION AND RECOMMENDATIONS

Primary angioplasty is superior to thrombolytic therapy for treating acute myocardial infarction, as evidenced by better patient outcomes and reduced mortality rates. Healthcare providers should prioritize primary angioplasty as the preferred treatment option for acute myocardial infarction to improve patient outcomes and decrease the burden of cardiovascular diseases. Further research on long-term benefits and cost-effectiveness is essential to strengthen the evidence base for clinical decision-making.

REFERENCES

1. Bullet IT. Warning signs of heart attack. Indian J Clin Pract. 2019 Sep;30(4):322-7.
2. ISIS-2 Collaborative Group. Second international study of infarct survival. Lancet. 1988;2:349-60.
3. Della GI, Miocardico SN. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet. 1986;1:397.
4. Granger CB, Califf RM, Topol EJ. Thrombolytic therapy for acute myocardial infarction: a review. Drugs. 1992 Sep;44:293-325.
5. Andersen HR, Nielsen TT, Rasmussen K, Thuesen L, Kelbaek H, Thayssen P, Abildgaard U, Pedersen F, Madsen JK, Grande P, Villadsen AB. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. New England journal of medicine. 2003 Aug 21;349(8):733-42.
6. Bonnefoy E, Lapostolle F, Leizorovicz A, Steg G, McFadden EP, Dubien PY, Cattan S, Boullenger E, Machecourt J, Lacroute JM, Cassagnes J. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomised study. The Lancet. 2002 Sep 14;360(9336):825-9.
7. Weaver WD, Simes RJ, Betriu A, Grines CL, Zijlstra F, Garcia E, Grinfeld L, Gibbons RJ, Ribeiro EE, DeWood MA, Ribichini F. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review. Jama. 1997 Dec 17;278(23):2093-8.
8. GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. New England Journal of Medicine. 1993 Nov 25;329(22):1615-22.
9. Grines CL, Browne KF, Marco J, Rothbaum D, Stone GW, O'Keefe J, Overlie P, Donohue B, Chelliah N, Timmis GC, Vlietstra RE. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. New England Journal of Medicine. 1993 Mar 11;328(10):673-9.

10. Zijlstra F, de Boer MJ, Hoorntje J, Reiffers S, Reiber J, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. New England Journal of Medicine. 1993 Mar 11;328(10):680-4.
11. Gibbons RJ, Holmes DR, Reeder GS, Bailey KR, Hopfenspirger MR, Gersh BJ. Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. New England Journal of Medicine. 1993 Mar 11;328(10):685-91.
12. Boer MD, Reiber JH, Suryapranata H, BRAND MV, Hoorntje JC, Zulstra F. Angiographic findings and catheterization laboratory events in patients with primary coronary angioplasty or streptokinase therapy for acute myocardial infarction. European heart journal. 1995 Oct 1;16(10):1347-55.
13. Meijer A, Verheugt FW, Werter CJ, Lie KI, Van der Pol JM, Van Eenige MJ. Aspirin versus coumadin in the prevention of reocclusion and recurrent ischemia after successful thrombolysis: a prospective placebo-controlled angiographic study. Results of the APRICOT Study. Circulation. 1993 May;87(5):1524-30.
14. Meier B, Ramamurthy S. Plaque sealing by coronary angioplasty. Catheterization and cardiovascular diagnosis. 1995 Dec;36(4):295-7.
15. Califf RM, Harrelson-Woodlief L, Topol EJ. Left ventricular ejection fraction may not be useful as an end point of thrombolytic therapy comparative trials. Circulation. 1990 Nov;82(5):1847-53.
16. Norris R, White H. Therapeutic trials in coronary thrombosis should measure left ventricular function as primary end-point of treatment. The Lancet. 1988 Jan 16;331(8577):104-6.
17. Simoons ML, Serruys PW, van den Brand M, Verheugt FW, Krauss XH, Remme WJ, Bär F, de Zwaan C, van der Laarse A, Vermeer F, Lubsen J. Early thrombolysis in acute myocardial infarction: limitation of infarct size and improved survival. Journal of the American College of Cardiology. 1986 Apr 1;7(4):717-28.
18. Simoons ML, Vos J, Tijssen JG, Vermeer F, Verheugt FW, Krauss XH, Cats VM. Long-term benefit of early thrombolytic therapy in patients with acute myocardial infarction: 5 year follow-up of a trial conducted by the Interuniversity Cardiology Institute of the Netherlands. Journal of the American College of Cardiology. 1989 Dec 1;14(7):1609-15.
19. Kloner RA. Coronary angioplasty: a treatment option for left ventricular remodeling after myocardial infarction?. Journal of the American College of Cardiology. 1992 Aug;20(2):314-6.
20. Morgan S, Smith H, Simpson I, Liddiard GS, Raphael H, Pickering RM, Mant D. Prevalence and clinical characteristics of left ventricular dysfunction among elderly patients in general practice setting: cross sectional survey. Bmj. 1999 Feb 6;318(7180):368-72.
21. Mehta RH, Eagle KA. Fortnightly review: Secondary prevention in acute myocardial infarction. Bmj. 1998 Mar 14;316(7134):838-42.
22. Campbell NC, Thain J, Deans HG, Ritchie LD, Rawles JM. Secondary prevention in coronary heart disease: baseline survey of provision in general practice. Bmj. 1998 May 9;316(7142):1430-4.
23. McCormick D, Gurwitz JH, Lessard D, Yarzebski J, Gore JM, Goldberg RJ. Use of aspirin, β-blockers, and lipid-lowering medications before recurrent acute myocardial infarction: missed opportunities for prevention?. Archives of internal medicine. 1999 Mar 22;159(6):561-7.