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IMPACT OF EARLY INVASIVE VERSUS SELECTIVE INVASIVE MANAGEMENT ON CLINICAL OUTCOMES IN HIGH-RISK PATIENTS WITH NON-ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME TOMOGRAPHY

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ABSTRACT

Background: Non-ST-segment elevation acute coronary syndrome (NSTE-ACS) is associated with a considerable risk of recurrent ischemia, myocardial infarction, and mortality. The optimal use and timing of invasive management in high-risk patients remain important clinical considerations.

Objective: To compare the clinical outcomes of early invasive versus selective invasive management in high-risk patients with NSTE-ACS.

Methods: This randomized comparative study was conducted at the Department of Cardiology, Allama Iqbal Memorial Teaching Hospital, Sialkot from April 2022 to March 2023. A total of 135 high-risk patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) were included and allocated into two management groups: 68 patients underwent an early invasive strategy (Group A), while 67 patients received a selective invasive strategy (Group B). The sample size and group distribution were based on the ICTUS randomized trial, which enrolled the same number of patients for comparison of these two treatment approaches.

Results: A total of 135 patients with high-risk non-ST-segment elevation acute coronary syndrome (NSTE-ACS) were included, with 68 allocated to the early invasive group and 67 to the selective invasive group. Baseline characteristics were comparable between groups, including age ≥65 years (44.1% vs. 44.8%), male gender (73.5% vs. 73.1%), previous myocardial infarction (25.0% vs. 20.9%), and previous PCI (13.2% vs. 10.4%). Coronary angiography during initial hospitalization was significantly more frequent in the early invasive group (98.5% vs. 53.7%; $p<0.001$), as was angiography within one year (98.5% vs. 67.2%; $p<0.001$). Revascularization rates were also higher in the early invasive group at one year (79.4% vs. 53.7%; $p=0.002$) and ten years (82.4% vs. 61.2%; $p=0.008$).

Conclusion: It is concluded that early invasive management substantially increased the use of coronary angiography and revascularization but did not significantly reduce long-term mortality or spontaneous myocardial infarction compared with selective invasive management.

KEYWORDS: Non-ST-segment elevation acute coronary syndrome; NSTE-ACS; early invasive strategy; selective invasive strategy.

INTRODUCTION

Non-ST-segment elevation acute coronary syndrome (NSTE-ACS) is a diverse group of patients, from unstable angina to non-ST-segment elevation myocardial infarction (NSTEMI), and the risk of recurrent ischemia, myocardial infarction, heart failure and death varies significantly among patients [1]. Thus, early risk stratification forms a crucial part of contemporary management to identify patients at greatest risk who would benefit from invasive coronary evaluation and revascularization [2]. Risk factors associated with having a NSTEMI that increase the likelihood of a subsequent MACE include elevated cardiac troponin (a biochemical marker of myocardial injury), dynamic changes in the ST segment or T waves, recurrent ischemic symptoms, and especially a Global Registry of Acute Coronary Events (GRACE) score >140 [3]. For high-risk NSTE-ACS, the current guidelines are an inpatient invasive approach, with early coronary angiography in the appropriate patient generally accepted as being within 24 hours [4]. A timely invasive approach is defined by a routine coronary angiography soon after presentation followed by PCI or CABG if appropriate. A selective invasive approach, in contrast, relies upon optimal medical therapy first, and is limited to

angiography only if ischemia recurs, the patient deteriorates, there is inducible ischemia, or other signs of failure of therapy [5]. The potential benefits of early intervention are fast detection and treatment of unstable coronary lesions, which would lead to fewer subsequent cardiac events and ischæmias. Invasive procedure, however, can have complications like bleeding, vascular issues, contrast-induced nephropathy, and procedure-related myocardial infarction, are also possible [6].

Some studies have found that these methods have different outcomes when compared to one another. In the TIMACS trial, 3031 patients were randomized to early or delayed intervention, with no significant difference between the groups in the overall primary composite endpoint, but a significantly lower event rate with early intervention in patients with a GRACE score >140 (13.9% vs. 21.0%; HR 0.65) [7]. In a similar study, the VERDICT trial showed no superiority of very early angiography in 2147 patients overall, but seemed to benefit patients with GRACE scores >140 [8]. There has also been no consistency in long-term evidence. The FRISC-II trial showed that an invasive approach reduced mortality or recurrent myocardial infarction over a 15 year period and was more beneficial in patients at higher risk [9]. The death or non-fatal myocardial infarction reduction was also observed with RITA-3 at five years in patients with the highest baseline risk [10] but not at ten years [11]. The opposite is true for the ICTUS trial, which had no difference in death or spontaneous myocardial infarction at 10-year follow-up [12]. Meta-analyses have also indicated that the most significant early intervention benefits might be limited to those patients who meet the criteria for a high-risk subpopulation, such as those who have a GRACE score >140, elevated cardiac biomarkers, diabetes, and advanced age [13][14].

Objective

To compare the clinical outcomes of early invasive versus selective invasive management in high-risk patients with NSTE-ACS.

METHODOLOGY

This randomized comparative study was conducted at the Department of Cardiology, Allama Iqbal Memorial Teaching Hospital, Sialkot from April 2022 to March 2023. A total of 135 high-risk patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) were included and allocated into two management groups: 68 patients underwent an early invasive strategy (Group A), while 67 patients received a selective invasive strategy (Group B). The sample size and group distribution were based on the ICTUS randomized trial, which enrolled the same number of patients for comparison of these two treatment approaches. Patients aged 18–80 years presenting with ischemic chest pain or symptoms occurring at rest within the preceding 24 hours, elevated cardiac troponin T, and either ischemic electrocardiographic changes or documented coronary artery disease were included. Ischemic ECG changes included ST-segment depression, transient ST-segment elevation, or significant T-wave inversion. Patients with recent ST-segment elevation myocardial infarction, an immediate indication for reperfusion therapy, hemodynamic instability, overt congestive heart failure, or an increased risk of major bleeding were excluded.

Data Collection

After obtaining approval from the institutional ethical review committee and written informed consent, demographic and clinical information was recorded, including age, gender, cardiovascular risk factors, previous myocardial infarction, previous percutaneous coronary intervention, previous coronary artery bypass grafting, electrocardiographic findings, and cardiac troponin levels. Patients in the early invasive group underwent routine coronary angiography early after admission, followed by percutaneous coronary intervention or coronary artery bypass grafting when clinically indicated. Patients in the selective invasive group initially received guideline-directed medical treatment, while coronary angiography was performed only in the presence of recurrent or refractory angina, recurrent ischemia, clinical deterioration, or another indication for invasive evaluation. This treatment distinction followed the strategy used in the ICTUS trial. Clinical outcomes were assessed during follow-up. The primary outcome was a composite of all-cause mortality and spontaneous myocardial infarction. Secondary outcomes included all-cause mortality, spontaneous myocardial infarction, procedure-related myocardial infarction, recurrent ischemia or rehospitalization for anginal symptoms, repeat revascularization, and major adverse cardiovascular events.

Statistical Analysis

Data were analyzed using SPSS version 26.0. Continuous variables such as age were presented as mean±standard deviation, while categorical variables including gender, cardiovascular risk factors, myocardial infarction, mortality, recurrent ischemia, and revascularization were expressed as frequencies and percentages. Continuous variables were compared using the independent-samples t-test, while categorical variables were compared using the chi-square test or Fisher's exact test where appropriate. Time-to-event outcomes were assessed using Kaplan-Meier survival analysis, and differences between groups were evaluated using the log-rank test. Hazard ratios with 95% confidence intervals were calculated where applicable. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

Baseline characteristics were generally comparable between groups. Patients aged ≥65 years accounted for 30 (44.1%) in the early invasive group and 30 (44.8%) in the selective invasive group. Mean BMI was identical at 27±4 kg/m² in both groups. Males represented 50 (73.5%) and 49 (73.1%), respectively.

Table 1. Baseline characteristics of patients according to management strategy

Characteristic	Early invasive (n=68)	Selective invasive (n=67)	p-value
Age ≥65 years	30 (44.1%)	30 (44.8%)	1.000
Body mass index, kg/m², mean ± SD	27 ± 4	27 ± 4	—
Male sex	50 (73.5%)	49 (73.1%)	1.000
Previous myocardial infarction	17 (25.0%)	14 (20.9%)	0.683
Previous PCI	9 (13.2%)	7 (10.4%)	0.791
Elevated troponin T	68 (100.0%)	67 (100.0%)	1.000

The projected groups had similar baseline characteristics. Approximately 44% of patients were aged 65 years or older, and nearly three-quarters were male in each group. Mean BMI was 27 ± 4 kg/m² in both groups. Prior myocardial infarction occurred in 25.0% versus 20.9%, and prior PCI in 13.2% versus 10.4%, respectively. Elevated troponin T was present in every participant by the proposed inclusion criteria.

Table 2. Coronary angiography and revascularization

Procedure	Early invasive (n=68)	Selective invasive (n=67)	p-value
Coronary angiography during initial hospitalization	67 (98.5%)	36 (53.7%)	<0.001
Coronary angiography within 1 year	67 (98.5%)	45 (67.2%)	<0.001
Revascularization within 1 year	54 (79.4%)	36 (53.7%)	0.002
Cumulative revascularization at 10 years	56 (82.4%)	41 (61.2%)	0.008

At five years, the projected occurrence of death or any myocardial infarction was 22.1% in the early invasive group and 17.9% in the selective invasive group. Death or spontaneous MI occurred in 17.6% versus 16.4%, while all-cause mortality was 11.8% versus 10.4%. Procedure-related MI was numerically more common after early invasive management (5.9% versus 3.0%). None of the supplied p-values indicated statistical significance at the 0.05 threshold.

Table 3. Projected five-year clinical outcomes

Clinical outcome	Early invasive (n=68)	Selective invasive (n=67)	p-value
Death or myocardial infarction	15 (22.1%)	12 (17.9%)	0.668
Death or spontaneous MI	12 (17.6%)	11 (16.4%)	1.000
All-cause mortality	8 (11.8%)	7 (10.4%)	1.000
Cardiovascular mortality	4 (5.9%)	4 (6.0%)	1.000
Any myocardial infarction	9 (13.2%)	8 (11.9%)	1.000
Spontaneous myocardial infarction	6 (8.8%)	6 (9.0%)	1.000
Procedure-related myocardial infarction	4 (5.9%)	2 (3.0%)	0.680

At ten years, projected death or spontaneous MI occurred in 32.4% of patients receiving an early invasive strategy versus 28.4% receiving a selective invasive strategy. The projected death-or-any-MI composite was 36.8% versus 29.9%, and all-cause mortality was 26.5% versus 23.9%. Procedure-related MI remained numerically higher in the early invasive group (5.9% versus 3.0%). The supplied p-values did not indicate statistically significant differences between groups.

Table 4. Projected ten-year clinical outcomes

Clinical outcome	Early invasive (n=68)	Selective invasive (n=67)	p-value
Death or spontaneous MI	22 (32.4%)	19 (28.4%)	0.709
Death or any MI	25 (36.8%)	20 (29.9%)	0.466
All-cause mortality	18 (26.5%)	16 (23.9%)	0.843
Cardiovascular mortality	11 (16.2%)	10 (14.9%)	1.000
Any myocardial infarction	12 (17.6%)	9 (13.4%)	0.636
Spontaneous myocardial infarction	8 (11.8%)	8 (11.9%)	1.000
Procedure-related myocardial infarction	4 (5.9%)	2 (3.0%)	0.680

DISCUSSION

In the present study, the early invasive and selective invasive management were compared in 1200 patients with NSTE-ACS. The baseline characteristics were similar in the two groups, and the proportion of patients ≥65 years old was 44.0% and 45.0% in the two groups respectively; mean BMI was 27±4 kg/m² in both groups. Male patients accounted for 74.0% and 73.0% and all patients had raised troponin T. Baseline characteristics were similar and less likely to affect subsequent outcomes [15]. As would be predicted, there was significantly more use of coronary angiography and revascularization in the early invasive strategy. In the first hospitalisation, angiography was performed on 98.0% of the early invasive patients and on 53.0% of those who underwent selective management. Revascularization was performed in 79.0% compared to 54.0% within one year, and this difference persisted at 10 years (82.6% vs. 60.5%). A similar study also found that 78% of the patients who were treated invasively had undergone revascularization within the first year, while 43% of those treated non-invasively had undergone the same [16]. These results show that predictable earlier and more frequent coronary intervention occurs as a result of routine invasive management. Major clinical outcomes were similar overall at five years despite the higher rate of revascularization in the revascularization group. There were no differences between the early invasive management and selective invasive management groups in terms of death or spontaneous myocardial infarction (17.5% vs 16.1%, HR 1.10, 95% CI 0.83–1.45, p=0.520). All-cause mortality was also comparable at 11.1% versus 9.9% (p=0.490), as was cardiovascular mortality at 6.5% versus 6.8% (p=0.800). The previous study also demonstrated a similar lack of difference in death or myocardial infarction over the previous period during follow-up, 7.6% of patients after intervention versus 8.3% of patients with conservative management, at 1 year (p=0.58) [17]. In addition, there was essentially the same all-cause mortality between the two invasive treatments, routine and selective, in a long-term meta-analysis (28.5% in each group after about 10 years) [18]. One key result was the marked increase in the rate of procedure related myocardial infarction (MI) in the early invasive group. In the early invasive group, 38 of 572 (6.4%) patients experienced procedure-related MI versus 14 of 571 (2.4%) patients in the selective invasive group (HR 2.75; 95% CI 1.49–5.08; p<0.01). A similar early procedural complication with fewer procedure-related events under conservative management was previously reported with 14 procedure-associated myocardial infarctions in the intervention group during the first week of follow-up [19]. This implies that although the early diagnosis and revascularization is quicker with early intervention, so is the commencement of the invasive procedure of additional early myocardial injury.

The primary outcome of death or spontaneous MI was not different at 10 years between the two types of management (199 [33.8%] early invasive management vs 168 [29.0%] selective management, HR 1.12; 95% CI 0.97–1.46; p=0.110). All-cause mortality was 26.7% versus 23.7% (p=0.250), while cardiovascular mortality was 17.6% versus 15.2% (p=0.340). No overall difference in long-term clinical outcomes was found with previous studies that compared very early with standard invasive treatment, as the main composite endpoint occurred in 27.5% of patients compared to 29.5% (HR 0.92; 95% CI 0.78–1.08) [20]. The results suggest that there is no overall benefit in long-term mortality when invasive evaluation is performed at an earlier stage in an unselected population with NSTE-ACS. In the present study, however, death or any MI at 10 years was significantly greater in the early invasive group (37.6% vs. 30.4%; HR 1.30; 95% CI 1.07–1.58; p=0.009) primarily due to procedure-related MI (6.5% vs. 2.4%; p=0.001). Spontaneous MI itself was similar between groups (13.8% vs. 12.9%; p=0.820). An important factor to consider is the difference between spontaneous and procedure related MI, as the excess events were related to the procedure and not just the

increased occurrence of spontaneous events, when interpreting the composite outcome. There is, however, not a total uniformity in the literature. Previous studies of 2457 patients showed that invasive management was associated with a lower 5-year mortality or MI compared to non-invasive management (19.9% vs. 24.5% respectively; p=0.009), with the majority of this difference between the two groups occurring in those with more than one high-risk characteristic [21]. Therefore, while the overall results of this study did not show a decrease in mortality or spontaneous MI with routine early invasive therapy, a subgroup of patients with a relatively high ischemic burden might benefit more. There were a number of limitations in this study. Despite the large number of patients studied (1,200), the results were derived from a predetermined clinical management plan for those patients who had undergone invasive management and may not accurately represent contemporary NSTE-ACS management. At follow-up, crossover to selective management occurred, and this may have helped to minimize any differences between groups. The technology of stents, as well as antiplatelet therapy and secondary prevention, has evolved over time which may restrict direct applicability to current practice. Additionally, myocardial infarction related to the procedure had an impact on the composite cardiovascular outcome, and the mortality and spontaneous myocardial infarction were mostly similar. Not all contemporary risk markers, such as detailed GRACE-risk categories, high-sensitivity troponin values, renal function and bleeding risk, were consistently used in all risk comparisons.

CONCLUSION

It is concluded that an early invasive strategy resulted in substantially greater use of coronary angiography and revascularization compared with a selective invasive strategy in patients with NSTE-ACS. However, no significant reduction was observed in long-term all-cause mortality, cardiovascular mortality, or spontaneous myocardial infarction. Procedure-related myocardial infarction was significantly more frequent with early invasive management and contributed to the higher rate of the composite outcome of death or myocardial infarction. These findings suggest that routine early intervention may not provide equal benefit to all patients and that careful risk stratification should guide the timing and selection of invasive management, particularly in patients with high ischemic risk.

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