Time to Medical Management in Patients Presenting with Non-ST Elevation Myocardial Infarction: A Retrospective Analysis of Two Teaching Hospitals

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Abstract

Background: It is clear that early administration of antiplatelet and antithrombotic therapy in patients presenting with Non-ST elevation MI (NSTEMI) is associated with improved outcomes. There are existing guidelines regarding early treatment in this patient population. We investigated how effectively patients are being managed for NSTEMI with respect to time to administration of indicated medical therapies in two teaching institutions.

Methods: A retrospective analysis was performed on 100 consecutive patients with no prior history of coronary artery disease who presented to the Emergency Departments of two teaching hospitals affiliated with McMaster University with the diagnosis of NSTEMI (defined as ischemic symptoms in presence of elevated cardiac biomarkers with or without electrocardiographic changes). Times of medication administration were obtained from the nursing notes.

Results: The mean age was 63.9 ± 14.1 years. The average time to administration of aspirin was 2.7 ± 4.3 hours, Unfractionated or Low Molecular Weight Heparin 5.4 ± 5.0 hours, and Clopidagrel 10.8 ± 16.5 hours from time of triage. Duration of symptoms prior to presentation were longer in patients with left ventricular (LV) dysfunction (on echocardiography assessed in 73 patients) compared to patients with normal LV, (7.5 h ± 8.3 vs. 3.3 h ± 3.4 p = 0.006). The average age of patients who had ASA, Heparin, and Clopidagrel initiated within 3 hours was lower than those after 6 hours (60.1 ± 12.7 years vs 68.1 ± 14.4 years, p = 0.01). The average age for those who underwent angiography ± percutaneous coronary intervention (PCI) was also lower at 60.2 ± 11.8 versus 76.1 ± 14.4 years (p = 0.0001).

Conclusions: There was a lag time in the administration of established medical therapies in patients presenting with first time NSTEMI. An age bias towards time to treat and selection for PCI may have also existed. The fact that increased duration of symptoms was associated with worse LV function may provide impetus for early recognition and management of patients with NSTEMI.

Introduction

There have been a number of studies that have demonstrated benefit of antiplatelet and antithrombotic therapies in the reduction of mortality and/or re-infarction rates in patients presenting with non ST-segment elevation myocardial infarctions (NSTEMI) and unstable angina [1–4]. In contrast, patients with ST segment elevation myocardial infarctions (STEMI) gain additional benefit from acute reperfusion therapy such as thrombolysis or primary percutaneous coronary intervention (PCI) in addition to the above therapies [5].

In the STEMI literature, there is clear survival benefit with early administration of thrombolytics or primary PCI, leading to early reperfusion and minimizing myocardial necrosis [6,7]. Although evidence regarding time to administration of antiplatelet and anticoagulant therapies in patients with unstable angina and NSTEMI is limited, the rationale would be to stabilize the unstable atherosclerotic plaque as soon as possible to minimize myocardial damage. The 2002 American College of Cardiology (ACC) guidelines recommend that therapies such as Aspirin, should be administered as soon as the patient presents with symptoms suggestive of the diagnosis [8].

The purpose of this study is to determine the time to initiation of effective medical therapies in patients presenting to two Emergency Departments (ED), affiliated with McMaster University, with
first presentation of NSTEMI. In addition, the purpose is to determine whether time to administration of medical therapy is associated with in-hospital mortality, re-ischemic episodes during indexed hospitalization, or evidence of myocardial dysfunction demonstrated by echocardiography. Lastly, subgroup analysis will be performed to determine subpopulations that were less likely to be treated with early medical therapy or to be referred for cardiac angiography.

**Methods**

After approval from the University research ethics board, a retrospective analysis was performed on 100 consecutive adult (≥18 years) patients with no previous history of coronary artery disease from (January 2004 to November 2005), admitted through the emergency departments of two McMaster University teaching hospitals with their first presentation of NSTEMI. The hospitals in this study included McMaster University Medical Centre (MUMC) and Hamilton General Hospital (HGH), a larger primary cardiac centre, both affiliated with the Hamilton Health Sciences Centre (HHSC) at McMaster University in Hamilton, Ontario. These two hospitals are located in the same city within 4 km of each other and routine transport of patients for cardiac catheterization is part of clinical practice and occurs in under 45 minutes.

Patients with no prior history of coronary artery disease were chosen for this study to eliminate any bias from the treating emergency department physicians based on past medical history. The diagnosis of NSTEMI in this study was defined as symptoms suggestive of acute coronary syndrome, in the presence of positive cardiac markers (troponin I or T), with or without ischemic changes on presenting electrocardiogram (ECG) [8]. Only patients presenting to the emergency departments were included in this study. Exclusion criteria included patients with past history of coronary artery disease (including stable angina and history of myocardial infarctions), significant cognitive dysfunction who were unable to give an adequate detailed history, and patients presenting with other acute co-morbidities such as exacerbation of chronic obstructive lung disease, infections, strokes, End-stage renal disease, etc.

Data collected included age, past medical history, traditional cardiac risk factors (history of hypertension, dyslipidemia, Diabetes Mellitus, Smoking, and Family history of premature coronary artery disease), symptoms and their duration prior to arrival at the ED, Killip classification [9], Thrombolysis in Myocardial Infarction (TIMI) risk score (Table 1) [10], presenting electrocardiogram, initial vital signs, up to three sets of cardiac biomarkers (troponin I or T and creatinine kinase), time of collection of cardiac biomarkers, initiation of intravenous nitroglycerin in the ED, initiation of intravenous furosemide in ED. A positive Troponin was defined as Troponin T > 0.04 µg/L or Troponin I > 0.5 µg/L [11].

Time to administration of medical therapy was calculated by the difference in time from patient presentation (time of triage) to time of administration of medications. This information was obtained from the nursing notes in ED records. Time to initiation of medical therapies was obtained for antiplatelet therapies (aspirin and clopidagrel), anticoagulants (unfractionated heparin or low molecular weight heparin), anti-anginal therapies (beta-blockers and intravenous nitroglycerin), ACE inhibitors or angiotensin receptor blockers, and antihyperlipidemic therapies (statins).

Routine post admission echocardiographic evaluation of left ventricular ejection fraction (LVEF) was performed as per the American Society of Echocardiography recommendations [12]. Grade I LV was defined as normal ejection fraction (≥55%), Grade II was defined as LVEF 45%–54%, Grade III was defined as LVEF 30–44%, and Grade IV was defined as LVEF ≤30%.

We also reviewed the records of patients referred for cardiac catheterization including time interval to catheterization, concomitant PCI, and referrals for urgent coronary artery bypass graft (CABG) surgery.

LVEF was obtained from in-hospital echocardiogram reports. In-hospital events such as development

**Table 1. Components of the TIMI risk score.**

| Component                                      |
|------------------------------------------------|
| Age ≥65 years                                  |
| ≥3 risk factors for CAD                        |
| Significant coronary artery stenosis (>50%)    |
| ST segment depression                           |
| Severe angina symptoms                          |
| Aspirin use in the last 7 days                  |
| Elevated serum cardiac markers                  |

CAD = coronary artery disease.
of congestive heart failure requiring intravenous furosemide administration, in-hospital ischemic episodes (defined as anginal chest pain with or without ECG changes), and in-hospital death were recorded. Other events recorded included significant hemorrhage defined as bleeding necessitating the transfusion of at least 2 units of blood [2], and infections which was defined as fever and positive blood cultures, or pulmonary infiltrate seen on chest X-ray.

Subgroup analysis was used to determine if there were any subpopulations that were often treated late with medical therapy, or preferentially referred for cardiac catheterization.

The data collected was expressed as means and standard deviations. Pearson correlation was used to determine any associations between the variables. T-tables were also used to compare means. A statistical analysis was performed using SPSS 11.0 (Chicago, Illinois).

Results
Data from 100 patients was analyzed. Mean age of the patients was 63.9 ± 14.1 years. Sixty three percent of patients were male. Fifty five percent of patients were admitted to the Hamilton General Hospital, and the remaining 45% were at McMaster University Medical Centre. The average number of cardiac risk factors was 1.8 ± 1.0. Table 2 demonstrates the demographic information for the study populations.

Majority of patients presented with classical anginal symptoms with 93% presenting with retrosternal chest pain. The average duration of symptoms prior to presentation to the ED was 9.8 ± 18.1 hours (n = 82). Average TIMI risk score [10] was 2.5 ± 0.9 in the study patients, whereas the average Killip Class was 1.2 ± 0.5. Eighty one percent of patients were in Killip class I, 15% in class II, and 4% in class III.

Twenty six percent of patients had normal presenting Electrocardiograms, 35% of patients had ST segment depressions, 40% of patients had T wave inversions, and 8% had Q waves. Further, 1% of patients had a Left Bundle Branch block. Seventy one percent of the patients had a first diagnostically positive cardiac troponin. The average time to collection of first Troponin was 0.9 ± 0.8 hours from time of triage in the ED.

Table 2. Baseline Demographics of patients presenting with non-ST elevation myocardial infarction.

|                          |     |
|--------------------------|-----|
| Diabetes Mellitus (Type I)| 1%  |
| Diabetes Mellitus (Type II)| 18% |
| *Hypertension             | 47% |
| *Dyslipidemia             | 29% |
| *Current Smoker           | 39% |
| *Family History of early CAD† | 26% |
| *History of smoking       | 29% |
| *CVA/TIA‡                | 7%  |
| *Peripheral Vascular Disease | 1%  |
| *Chronic Obstructive Lung Disease | 4%  |
| *Atrial Fibrillation      | 3%  |
| Medications:              |     |
| Aspirin                   | 18% |
| Beta-Blockers             | 13% |
| ACE inhibitors or ARBs    | 20% |
| HMG CoA reductase inhibitors | 13% |
| Average number of Cardiac Risk Factors | 1.8 ± 1.0 |
| Average TIMI Risk score on Presentation | 2.5 ± 0.9 |
| Average Duration of Symptoms prior presentation to ED | 9.8 ± 18.1 hours (n = 82) |

*Documented by patient history, †Family history of coronary artery disease, diagnosed in first degree relative at the age of 45 years or younger in males, and 55 years or younger in females, ‡Any history of cerebrovascular accident (CVA) or transient ischemic attack (TIA). ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; ED, emergency department; HMG Co-A; 3-hydroxy-3-methylgluteryl coenzyme A, TIMI, thrombolysis in myocardial infarction.
patients had a positive second troponin, with an average time to collection of 8.6 ± 3 hours.

Twenty percent of patients received Aspirin before arriving at the ED by either emergency medical services, family physician or from home. For the other 80 patients, the average time from ED triage to administration of Aspirin was 2.7 ± 4.3 hours. The average time to administration of Clopidogrel was 10.8 ± 16.5 hours, (n = 98). The average time to administration of low molecular weight heparin or intravenous unfractionated heparin was 5.4 ± 5.0 hours, (n = 97). The average time to administration of beta blockers (oral or intravenous), was 12.3 ± 20.3 hours (n = 92), and the average time to administration of ACE inhibitors or angiotensin receptor blockers (ARBs) was 20.5 ± 15.5 hours, (n = 89) (see Table 3).

Seventy three percent of patients had an in-hospital Echocardiogram. Of these patients, 48/73 (65.8%) had a grade I left ventricular (LV) function, 26% had grade II LV, 8.2% had grade III LV. None of the patients had a grade IV LV on echocardiogram. In total, 25 out of 73 patients (34%) had evidence of Grade II LV function or worse.

Cardiac catheterization
Seventy seven percent of patients were referred for cardiac catheterization. The average wait time for cardiac catheterization was 3.9 ± 3.5 days. Percutaneous coronary intervention (PCI) was performed in 50 out of those 77 patients referred (65%).

Five out of the 77 patients referred for cardiac catheterization had normal epicardial coronary arteries (6.5%), 10 patients had triple vessel disease and three patients had left main disease. Eleven percent of all hospitalized patients were referred for urgent CABG surgery. The average length of stay for patients not requiring CABG was 7.3 ± 4.3 days (n = 89).

Complications
There were no in hospital deaths. Out of the 100 admitted patients, 3% developed rapid atrial fibrillation, 24% of patients experienced recurrent ischemic chest pain, 8% of patients required intravenous nitroglycerin for their recurrent pain, 8% developed pulmonary edema requiring intravenous furosemide administration, and 3% developed bradycardia requiring administration of atropine or insertion of a temporary pacemaker.

There was no significant association between time to initiation of either antiplatelet or anticoagulant therapy, or average time to antiplatelet and anticoagulant therapy with the above mentioned complications.

Only one person developed a retroperitoneal hemorrhage. There were no other significant hemorrhagic episodes. One patient developed Heparin induced thrombocytopenia, and 3% developed an infection requiring intravenous antibiotics administration.

In a subgroup analysis (Table 4), patients with significant LV dysfunction, (defined by Grade II or worse LV function), had longer duration of symptoms prior to presenting to the ED when compared to patients with normal LV function, (7.5 ± 8.3 hours, n = 19 vs. 3.3 ± 3.4 hours, n = 43 respectively; p = 0.006). The There was a significant age discrepancy (Table 5) with respect to which patients were referred for cardiac catheterization (60.2 ± 11.8 years, n = 77 vs. 76.1 ± 14.4 years, n = 23; p < 0.05). In another subgroup analysis (Table 6), the mean time to administration of aspirin, clopidogrel, and heparin was calculated for each patient. In this analysis, only 37%

| Table 3. Time to Administration of effective medical therapies in patients presenting with non-ST elevation myocardial infarction from time of triage. |
|---------------------------------------------------------------|
| **Time to administration (hours)** | **N (Total N = 100)** |
| Aspirin | 2.7 ± 4.3 | 80* |
| Clopidagrel | 10.8 ± 16.5 | 98 |
| Heparin (Unfractionated or LMWH) | 5.4 ± 5.0 | 97 |
| Beta-Blockers† | 12.3 ± 20.3 | 92 |
| ACE Inhibitors or ARBs‡ | 20.5 ± 15.5 | 89 |

*20% of patients received aspirin prior to presentation to ED; †Intravenous or oral beta-blockers; ‡Angiotensin receptor blockers (ARBs).
of all patients were treated with antiplatelet and antithrombotic medications with a mean time less than three hours from presentation to the emergency department. In addition, the majority of patients who were treated at a mean time beyond six hours were significantly older in age.

Discussion
In this study, there was a clear delay in the administration of antiplatelet and anticoagulant therapy in patients presenting with NSTEMI. The majority of patients presented to the emergency departments with classic anginal symptoms, electrocardiograms with ischemic changes, and first positive cardiac biomarker that was available within the first two hours from triage. All patients had either positive cardiac biomarkers or other high risk features which automatically put them into higher risk categories [10]. Thus, time to diagnosis could not explain the entire delay in initiation of treatment.

There are a number of hypotheses that can account for the delay in therapy. These can range from time for the ED physician to see the patient, time for the ED physician to reassess the patient after reviewing lab results, time for nurses to obtain and administer medication orders, and time to receive medications from the pharmacy. In many instances, the ED physician requested a consultation from internal medicine or cardiology services prior to initiating established therapies.

Although this study demonstrated increased lapsed time to initiate medical management in NSTEMI patients, it still remains unclear whether this delay is associated with worse long-term outcomes, such as death, stroke, or recurrent myocardial infarctions.

There is now mounting evidence that early administration of antiplatelet and antithrombotic therapies is associated with significant benefit in patients presenting with NSTEMI [2,11,13]. Albeit when compared to STEMI this evidence is not as robust. In patients with STEMI, there is ample evidence that suggest prompt recanalization of the infarct related artery via either primary PCI or thrombolysis leads to improved clinical outcomes [14,15]. The ISIS-2 investigators demonstrated that early administration of 160 mg of ASA showed improved benefit in acute coronary syndromes [16].

In studies of patients with unstable angina (UA) and NSTEMI, one randomized double-blinded placebo control study found that early administration of aspirin and heparin when compared to placebo, lead to a significant reduction in refractory angina and myocardial infarction in

Table 4. Comparison of subgroups of patients with normal and abnormal left ventricular systolic function on echocardiogram.

|                     | Normal LV (n = 48) | Grade II LV (n = 25) | p value |
|---------------------|-------------------|---------------------|---------|
| Age                 | 62.7 ± 12.9 y     | 67.9 ± 15.2 y       | 0.12    |
| TIMI Risk Score     | 2.5 ± 0.9         | 2.8 ± 0.9           | 0.19    |
| Killip Class        | 1.1 ± 0.2         | 1.6 ± 0.8           | <0.01   |
| Symptom Duration    | 3.3 ± 3.4 h       | 7.5 ± 8.3 h         | <0.01   |
| Cardiac Risk Factors| 1.8 ± 1.0         | 1.8 ± 1.0           | 0.9     |
| Peak CK             | 359.8 ± 357.7     | 571.4 ± 623.7       | 0.6     |

CK = creatinine kinase.

Table 5. Comparison of subgroup of patients with referral to cardiac catheterization for possible percutaneous intervention.

|                 | Cath (n = 77) | No cath (n = 23) | p value |
|-----------------|--------------|-----------------|---------|
| Age             | 60.2 ± 11.8 y| 76.1 ± 14.4 y   | <0.01   |
| TIMI Risk Score | 2.5 ± 1      | 2.6 ± 0.7       | 0.6     |
| Killip Class    | 1.2 ± 0.5    | 1.4 ± 0.6       | 0.2     |
patients with UA. In this study, unfractionated heparin and aspirin were administered as soon as possible when patients presented to the ED [17]. In the CURE trial, the efficacy of Clopidagrel in patients with UA/NSTEMI was demonstrated within the first few hours after randomization suggesting benefit with early administration of dual antiplatelet therapy [2]. This effect was still substantial despite randomization occurring within 24 hours from symptom onset.

In our study, patients who waited before presenting to the ED with chest pain tended to have a higher incidence of LV dysfunction on echocardiogram. This finding may suggest that long periods of untreated ischemic time may lead to more myocardial damage. Thus, this may argue in favor of initiating antiplatelet and antithrombotic therapy as soon as the patient presents to the ED with symptoms suggestive of NSTEMI or UA. However, LVEF was not known prior to hospitalization, and measurement of in-hospital LV function could have been a marker of stunned myocardium rather than long term LV dysfunction.

Overall, considering that NSTEMI patients with significant degree of LV dysfunction, may have similar mortality rates to STEMI patients [18], and that administration of antiplatelet and antithrombotic therapies are relatively easy with minimal side effects and consequences, prompt administration of medical therapy should be encouraged in NSTEMI or UA patients until more evidence becomes available.

A possible bias towards elderly patients was apparent in this study. Elderly patients were less likely to be referred for cardiac catheterizations. In addition, elderly patients were more likely to be treated with antiplatelets and antithrombetics later from the time of triage. This could have a significantly negative consequence considering older patients are at a higher risk, and may benefit from a more aggressive treatment strategy [5]. This has also been described in other retrospective quality assurance studies [19]. Although in our study majority of patients did receive appropriate therapy based on the recommendations made by the governing bodies [11] the major discrepancy was the timing of initiation of therapies. Considering that McMaster University is one of the leaders in the field of evidence-based medicine, this probably reflects the closest level of practice to the guidelines.

Earlier studies may have suggested that elderly patients were prone to complications from coronary angiography [20]. However, more recent studies taking into account of improved operator skill and technology have found no significant difference in morbidity and mortality in elderly patients when compared to younger patients [21,22].

**Limitations**

As a retrospective cohort study, it was difficult to eliminate all sources of bias. In addition, times between the two ED, including the nurses that were documenting patient charts were not standardized. Valuable data was not available in all study patients.

Our study did not demonstrate that time to administration of medical therapy in NSTEMI patients was associated with hard endpoints such as stroke or death. Follow-up data was not assessed in this study; therefore re-infarction rates are not available. In addition, LV function was measured one time during the index admission into hospital. Poor LV function could have been a marker of stunned myocardium rather than myocardial damage from the NSTEMI.

**Conclusions**

Early diagnosis was established in the majority of NSTEMI patients. However, there was a lag time in administration of established and effective therapies. Although there is no direct evidence, the fact that increased duration of symptoms was

| Table 6. Mean time to administration of Aspirin, Clopidagrel, and Heparin. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Age (years)                     | 60.1 ± 12.7     | 63.2 ± 14.3     | 68.1 ± 14.4     | 0.01*           |
| Cardiac Risk Factors            | 2.2 ± 0.9       | 1.4 ± 0.9       | 1.8 ± 0.9       | NS              |
| TIMI Risk Score                 | 2.8 ± 0.9       | 2.3 ± 0.9       | 2.4 ± 0.9       | NS              |

*Between <3 hours and >6 hours groups.
associated with decreased LV systolic function, and that administration of antiplatelets and antithrombotics are relatively easy and safe, early recognition and management with effective therapies should be recommended in patients presenting with NSTEMI and UA to the emergency departments.

Disclosure
The authors report no conflicts of interest.

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