A systematic review and meta-analysis on the effectiveness of an invasive strategy compared to a conservative approach in elderly patients with non-ST elevation acute coronary syndrome

Joan Dymphna P. Reaño, MD[1], Maria Grethel C. Dimalala, MD[2], Louie Alfred B. Shiu, MD[3], Karen V. Miralles, MD[3], Noemi S. Pestaño, MD[3], Felix Eduardo R. Punzalan, MD[3], Bernadette Tumanan-Mendoza, MD[3], Michael Joseph T. Reyes, MD[3,4], Rafael R. Castillo, MD[3,5,6]

[1] Fellow in Adult Cardiology, Manila Doctors Hospital, Manila, Philippines

[2]Fellow in Interventional Cardiology, Manila Doctors Hospital, Manila, Philippines

[3] Consultant in Adult Cardiology, Manila Doctors Hospital, Manila, Philippines

[4] Consultant in Interventional Cardiology, Manila Doctors Hospital, Manila, Philippines

[5]Professor in Cardiovascular Medicine, Adventist University of the Philippines, Silang, Philippines

[6]Dean Emeritus, FAME Leaders Academy, Makati, Philippines

Correspondence to:

Dr. Joan Dymphna P Reaño, Manila Doctors Hospital, 667 United Nations Avenue, Ermita, Manila, Philippines

Email address: jdp.reano@gmail.com; medicalfiles.inquirer@gmail.com

Mobile tel. no.: +63 917 5089 757

Short/running title: Management strategies in elderly with NSTEMI

ABSTRACT

Background: Elderly patients, 65 years old and older, largely represent (>50 %) of hospital-admitted patients with acute coronary syndrome (ACS). Data are conflicting comparing efficacy of early routine invasive (within 48-72 hours of initial evaluation) versus conservative management of ACS in this population.

Objective: We aimed to determine the effectiveness of routine early invasive strategy compared to conservative treatment in reducing major adverse cardiovascular events in elderly patients with non-ST elevation (NSTE) ACS.

Data Sources: We conducted a systematic review of randomized controlled trials through PubMed, Cochrane, and Google Scholar database.

Study Selection: The studies included were randomized controlled trials that evaluated the effectiveness of invasive strategy compared to conservative treatment among elderly patients $\geq$ 65 years old diagnosed with NSTEACS. Studies were included if they assessed any of the following outcomes of death, cardiovascular mortality, myocardial infarction (MI), stroke, recurrent angina, and need for revascularization. Five articles were subsequently included in the meta-analysis.

Data Extraction: Three independent reviewers extracted the data of interest from the articles using a standardized data collection form that included study quality indicators. Disparity in assessment was settled by an independent adjudicator.

Data Synthesis: All pooled analyses were based on fixed effects model. A total of 2,495 patients were included, 1337 in the invasive strategy group, and 1158 in the conservative treatment group.

Results: Meta-analysis showed less incidence of revascularization in the invasive (2%) over conservative treatment groups (8%), with overall risk ratio of 0.31 (95% CI 0.16-0.61, I^2 =0%). There was also less incidence of stroke in the invasive (2%) versus conservative group (3%) but this was not statistically significant. A significant benefit was noted in the reduction of all-cause

mortality (RR 0.63, 95% CI 0.55-0.72, I^2=84%) and myocardial infarction (RR 0.62, 95% CI 0.49-0.79, I^2=63%) but with significant heterogeneity.

Conclusion: There was a significantly lower rate of revascularization in the invasive strategy group compared to the conservative treatment group. In the reduction of all-cause mortality and MI, there was benefit favoring invasive strategy but with significant heterogeneity. These findings do not support the bias against early routine invasive intervention in the elderly group with NSTEACS. However, further studies focusing on the elderly with larger population sizes are still needed.

Keywords: *Elderly, non-ST Elevation myocardial infarction, acute coronary syndrome, invasive strategy, conservative treatment, coronary artery disease, ACS MACE, CVD in Philippines*

I. INTRODUCTION

Based on the World Health Organization's Global Burden of Disease report, ischemic heart disease (IHD) is the overall leading cause of death worldwide.[1] Although the annual number of hospital discharges for acute coronary syndromes (ACS) in developed countries has declined slowly over the past two decades, the number has increased in developing countries.[2] In the Philippines, cardiovascular disease (CVD) remains the leading cause of mortality.[3] The Philippine Heart Association ACS registry reported that ACS is prevalent in the age range 51-70, with mean age group of 66 years old. [3]

The most recent American College of Cardiology/American Heart Association (ACC/AHA 2014) and the European Society of Cardiology (ESC 2015) guidelines for non–ST segment elevation ACS (NSTEACS) reflect medical advancements in therapeutics and strategies of care leading to improved survival in ACS, but this was mainly observed in relatively younger individuals (<65 years of age) and in men. These guidelines emphasize intensive and early medical and interventional therapy, particularly for those at high risk.[4,5,6]

The 2014 AHA/ACC NSTEACS Guidelines generally recommend that older patients with NSTEACS should be treated with goal-directed medical therapy, together with an early invasive strategy, and revascularization as appropriate.[5] The 2015 ESC Guidelines for the Management of ACS, on the other hand, recommend that decisions on elderly patients with NSTEACS should be based on ischemic and bleeding risks, estimated life expectancy, comorbidities, quality of life, patient values and preferences, and the estimated risks and benefits of revascularization.[6] Despite the guidelines, older patients are less likely to undergo procedures after an NSTEACS than younger patients due in part to patient and practitioner concerns about the increased risk of complications.[7,8,9]

Due to conflicting results of studies, lack of specific recommendations from the abovementioned guidelines, and the paucity of data on early invasive strategy versus conservative treatment for NSTEACS in elderly patients, this meta-analysis was conducted to focus on this special population to compare benefits and risks of early invasive therapy versus conservative management.

II. RESEARCH QUESTION

Among elderly patients aged ≥ 65 years old with NSTEACS, how effective is invasive strategy compared to conservative treatment in preventing major adverse cardiovascular events (MACE)?

III. OBJECTIVES

General: To determine the effectiveness of invasive strategy compared to conservative treatment in reducing MACE among elderly patients with NSTEACS.

Specific:

Among elderly patients with NSTEACS, to determine the effectiveness of invasive strategy compared to conservative treatment, in 6 months (short-term) to 3 years (long-term), in reducing:

a. Death or all-cause mortality;
b. Cardiovascular mortality;
c. Myocardial infarction (MI);
d. Stroke;
e. Recurrent angina;
f. Need for revascularization.

IV. METHODOLOGY

Study Registration

Prior to the conduct of the research, the study was registered and approved by the Committee on Research (CORES) of Manila Doctors Hospital.

Criteria for considering studies for this review

The studies included were randomized controlled trials that evaluated the effectiveness of invasive strategy compared to conservative treatment among elderly patients $\geq$ 65 years old diagnosed with NSTEACS. Studies were included if any of the outcomes assessed were: death, cardiovascular mortality, MI, stroke, recurrent angina, and need for revascularization.

Definition of terms:

1. **Invasive strategy or early invasive strategy** –Routine early (within 48-72 hours of initial evaluation) cardiac catheterization, followed by PCI, CABG, or continuing medical therapy, depending on the coronary anatomy.

2. **Conservative treatment** - Initial optimal medical management, with cardiac catheterization reserved for patients with recurrent ischemia at rest or after a non-invasive stress test, followed by revascularization if the anatomy is suitable.
3. **Elderly patients** – Patients aged 65 years or older (WHO, 2000), with or without comorbidities.
4. **Non-ST elevation acute coronary syndrome (NSTEACS)** – Unstable angina, with or without ST segment depression on electrocardiogram with normal or raised blood concentration of troponin T or I. Elevated troponin was defined as a value exceeding the 99th percentile of a normal population at the local laboratory at each participating site.

Search methods for identification of studies

Systematic computerized search (APPENDIX A) was performed using the Pubmed and Cochrane databases. MESH and free text of the following main key terms were used: "randomized controlled trials", "elderly", "non-ST elevation acute coronary syndrome", "invasive strategy", "conservative management", "invasive strategy versus conservative strategy", "major adverse cardiovascular events", "all-cause mortality", "cardiovascular mortality", "myocardial infarction", "stroke", "recurrent angina", "need for revascularization". The last search was done on 10 August 2017.

Eligibility assessment was performed independently in an unblinded standard manner by three reviewers. The literature search identified 322 possible articles. Of these, 69 were relevant, particularly they involved studies related to ACS. Prospective cohort studies and post hoc analyses were excluded. Of the 69 articles, 55 were excluded due to different intervention since they did not involve comparing invasive versus conservative management in ACS. After assessing 14 articles for eligibility, 8 articles with different population and methods were excluded (details for the titles of the studies and reasons for exclusion are listed in APPENDIX D). One article was possibly

eligible but did not report the event rates per treatment group. To access needed data in this particular study, correspondence with the author via email was done, but with no reply from the author until the time of writing. Five articles were subsequently included in the meta-analysis (Figure 1).

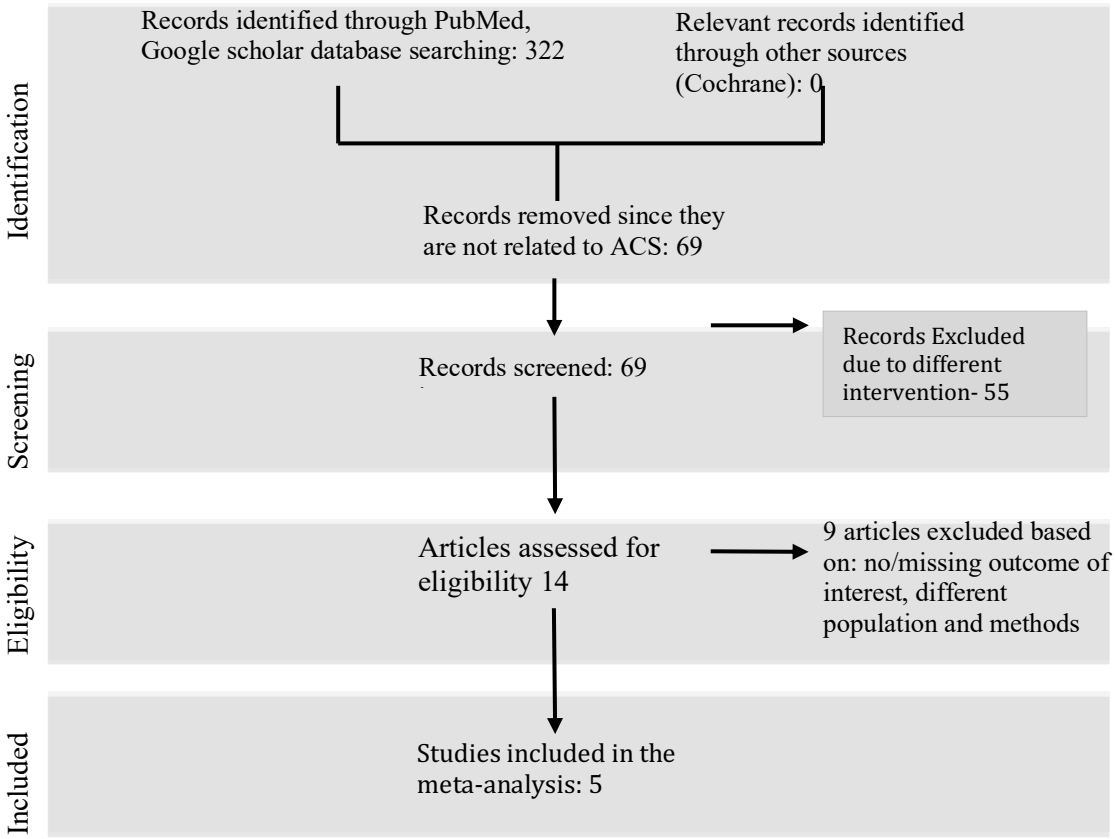

Figure 1. Search strategy for identification of studies

Assessment of risk bias of included trials:

Three independent reviewers extracted the data of interest using a standardized data collection form and individually appraised each trial. The reviewers discussed the quality of included trials, outcomes to be collected, and risks of bias. Disparity in assessment was settled by an independent adjudicator. The assessment of random sequence generation, allocation concealment, incomplete outcome data, blinding of participants and personnel, blinding of outcome

163 assessment, and intention-to-treat analysis was done using the quality scale for meta-analytic
164 review, the Cochrane Collaboration Tool for Risk of Bias.
165
166 ***Data analysis***
167 Review Manager 5.3 was used to analyze the data. Analysis of dichotomous data was done
168 using risk ratio, 95% confidence interval, and Mantel-Haenszel method with fixed effects model.
169 Heterogeneity between trials was tested using a standard Chi-square test and I^2 statistics. The p-
170 value of <0.10 was considered to be statistically significant and I^2 of ≥50% is considered to have
171 high heterogeneity.
172
173 ***Description of studies***
174 Five randomized controlled trials involving a total of 2,495 patients met the inclusion
175 criteria. The data on population characteristics, intervention type, and measured outcomes were
176 extracted from each trial (Table 1). Four of the trials included elderly patients with NSTEACS
177 aged ≥ 70 years while one trial included patients ≥ 65 years old.[10] The studies compared the
178 effectiveness of early invasive strategy (treatment group) versus optimum medical treatment
179 (control group) in the management of NSTEACS in elderly patients.
180
181 **Table 1. Characteristics of included trials**

Study ID	Population		Intervention	Outcome	Methods
Sanchis et al., 2016 N= 106	**Inclusion:** Patients ≥ 70 years old with significant comorbidities	**Exclusion:** 1) Dynamic ST-segment changes; 2) Prior known non revascularizable CAD;	**Treatment Group:** Routine cardiac catheterization within 72 h of admission	**Primary:** Composite of all-cause mortality, recurrent myocardial infarction and	Open label multicenter randomized controlled trial

	diagnosed with NSTEMI	3) Concomitant heart disease different than ischemic heart disease; and 4) Life expectancy ≤1 year.	**Control Group:** Only medical treatment, although cardiac catheterization was allowed in the case of poor in-hospital outcome	readmission for cardiac cause **Secondary:** All-cause mortality, Reinfarction or Post-discharge revascularization, and bleeding episodes	(Follow-up of 3 to 36 months)
Tegn et. al, 2016 N= 457	**Inclusion:** Patients ≥ 80 years old with NSTEMI or Unstable Angina	**Exclusion:** 1) Clinically unstable; 2) Cardiogenic shock; 3) Continuing bleeding problems; or 4) Short life expectancy.	**Treatment Group:** Early coronary angiography (within 24 hours) with immediate assessment for adhoc PCI, CABG, or optimum medical treatment **Control Group:** Optimum medical treatment alone	**Primary:** Composite of MI, need for urgent revascularization stroke and death **Secondary:** Death from any cause	Open label multicenter randomized controlled trial (Follow-up of 3 years)
Puymirat et al., 2012 N=1,645 (total population)	**Inclusion criteria:** Men or women aged over 18 years (Includes	**Exclusion:** 1) Iatrogenic MI; 2) ACS diagnosis invalidated in favor	**Treatment Group:** Early coronary angiography **Control Group:**	**Primary:** Mortality, Minor bleeding, and Major bleeding	Open label multicenter randomized controlled trial

n= 658 (elderly subgroup)	Elderly Subgroup > 75 years old), who were admitted within 48 h after symptom onset for an acute MI	of another diagnosis; and 3) Patients with unstable angina and no increase in cardiac biomarkers.	Received only medical therapy		(Follow-up of 3 years)
Savonnito, et al, 2012 N=313	**Inclusion:** Patients ≥75 years old, assessed to have NSTEACS with cardiac ischemic symptoms at rest within 48 h	**Exclusion:** 1) Secondary causes of myocardial ischemia; 2) Ongoing myocardial ischemia or heart failure despite optimized therapy; 3) PCI or CABG within 30 days before randomization; 4) Serum creatinine >2.5 mg/dl; 5) Cerebrovascular accident within the previous month; 6) Recent transfusions;	**Treatment group:** Coronary angiography within 72 h and, when indicated, coronary revascularization by either PCI or CABG **Control Group:** Initially conservative therapy and coronary angiography during index hospital stay was allowed in the case of refractory ischemia, myocardial (re)infarction, heart failure of ischemic origin, or malignant	**Primary:** Composite of all-cause mortality, non-fatal MI, disabling stroke, and repeat hospital stay for cardiovascular causes or severe bleeding within 12 months	Open randomized controlled trial (Follow-up of 1 year)

		7) Gastrointestinal or genitourinary bleeding within 6 weeks before randomization; 8) Platelet count <90,000 cells/ul 9) Ongoing oral anticoagulation 10) Severe obstructive lung disease 11) Malignancy; 12) Neurological deficit limiting follow-up.	ventricular arrhythmias		
Bach et al., 2004 N=2, 220 (total population) n=962 (elderly subgroup)	**Inclusion:** Patients older than 18 years of age (with subgroup of ≥ 65 years old) with episode of angina in the preceding 24 hours; Candidates for coronary revascularization	**Exclusion:** 1) Persistent ST-segment elevation; 2) Secondary angina; 3) Percutaneous coronary revascularization or coronary bypass surgery within the previous 6 months;	**Treatment Group:** Coronary angiography 4 to 48 hours after randomization **Control Group:** Medical treatment; Coronary angiography was reserved for patients who had certain	**Primary:** Rates of 30-day and 6-month mortality, nonfatal MI, rehospitalization, stroke, and hemorrhagic complications	Open randomized controlled trial (Follow-up of 6 months and 1 year)

		4) Unstable comorbidities; 5) Left bundle-branch block or paced rhythm; 6) Severe congestive heart failure or cardiogenic shock; 7) Clinically important systemic disease; 8) Serum creatinine concentration greater than 220 umol/L (>2.5 mg/dL); 9) Treatment with a glycoprotein IIb/IIIa antagonist within the past 96 hours; or 10) Ongoing long-term treatment with ticlopidine, clopidogrel, or warfarin.	high-risk characteristics consistent with failure of medical therapy or stress-induced ischemia		

In the treatment arm, four trials specified the time to intervention (4-72 hours) [10,12,13,14]. Only one study did not specify the time to intervention but only mentioned "during initial

admission".[11] Two out of the five trials included CABG as part of the intervention when indicated.[12,13] In the control group all the trials used standard medical treatment .[10-14]

All trials assessed the outcome of all-cause mortality. All trials except one reported the outcome of myocardial infarction.[11] All trials except two assessed the outcome of stroke.[11,14] The outcomes of revascularization were reported by all except by two studies.[10,11] Lastly, the events of cardiovascular death and recurrent angina were assessed only by one study.[13]

The Cochrane collaboration tool was used to assess the risk of bias. The random sequence generation, allocation concealment, incomplete outcome data, blinding of participants and personnel, blinding of outcome assessment, and intention-to-treat analysis were evaluated for each trial. All included trials were assessed to have low risk for bias (Table 2).

Table 2. Quality assessment table

Study ID	Method of Random Sequence Generation (Selection Bias)	Method of Allocation Concealment (Selection Bias)	Incomplete Outcome Data/Loss of participants to follow up (Attrition Bias)	Blinding of Participants and Personnel (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Selective Reporting/ Intention to treat analysis (Reporting Bias)
Sanchis et al., 2016	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Tegn et. Al, 2016	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

Puymirat et al., 2012	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Savonnito, et al, 2012	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Bach et al., 2004	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

V. RESULTS

Effects of intervention on outcomes of interest

A. All-cause mortality

A total of 242 among 1338 (18 %) elderly patients with NSTEACS died in the Invasive Strategy Group; while 296 died among 1158 (26 %) patients in the Conservative Group (Figure 2). The pooled analysis of all-cause mortality showed statistically significant benefit of invasive over conservative strategy with an overall risk ratio of 0.63 (95% CI 0.55 to 0.72) but with significant heterogeneity (p value of 0.0001, I^2 =84%).

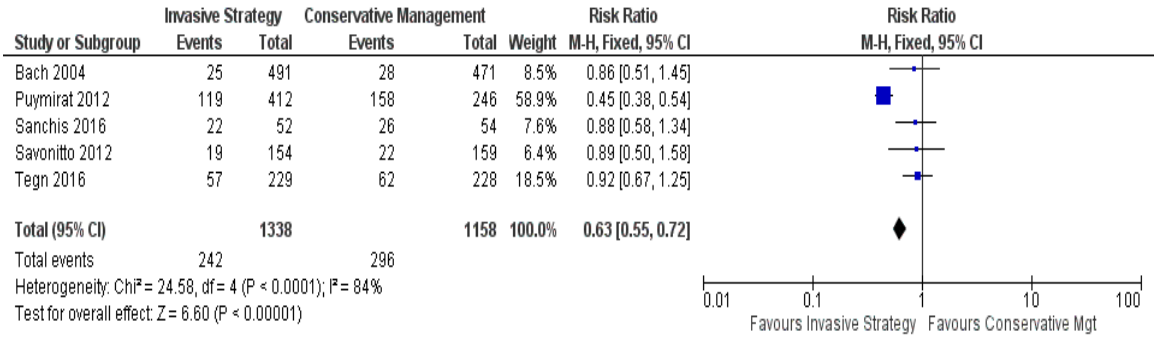

Figure 2. Comparison between invasive and conservative strategy with the outcome of all-cause mortality

B. Myocardial infarction

In the Invasive Strategy Group, there were 89 events of MI among a total of 926 (10 %) patients; while there were 142 among 912 (16 %) patients in the Conservative Group (Figure 3). The pooled analysis showed that invasive strategy is beneficial over conservative treatment in preventing MI with an overall risk ratio of 0.62 (95% CI 0.49 to 0.79) but with significant heterogeneity (p value of 0.0001, $I^2 = 63\%$).

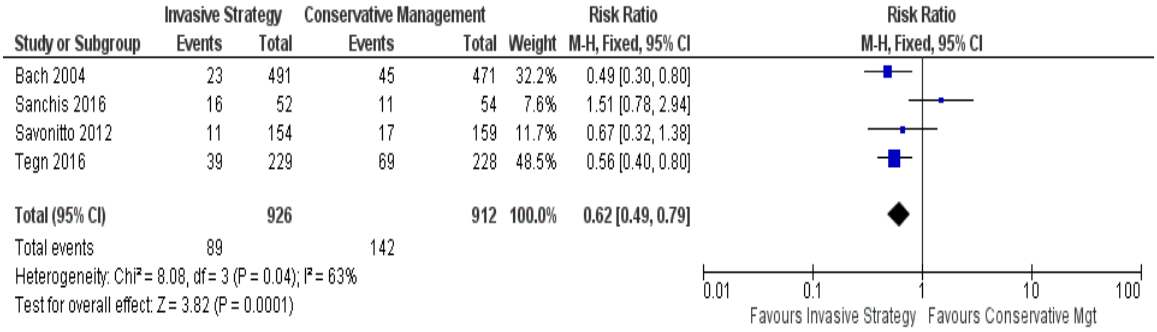

Figure 3. Comparison between invasive and conservative strategy with the outcome of myocardial infarction

C. Stroke

Among the five trials, Savonitto et al. (2012), Tegn (2016), and Bach (2004) reported the outcomes of stroke (Figure 4). In the Invasive Strategy Group, there were 13 events of stroke among 874 (2%) patients; while there were 24 among 858 (3%) patients in the Conservative Group. The pooled analysis showed that early invasive strategy was favored over conservative treatment in preventing stroke but no statistically significant benefit with overall risk ratio of 0.53 (95% CI 0.27-1.03, $I^2 = 0\%$).

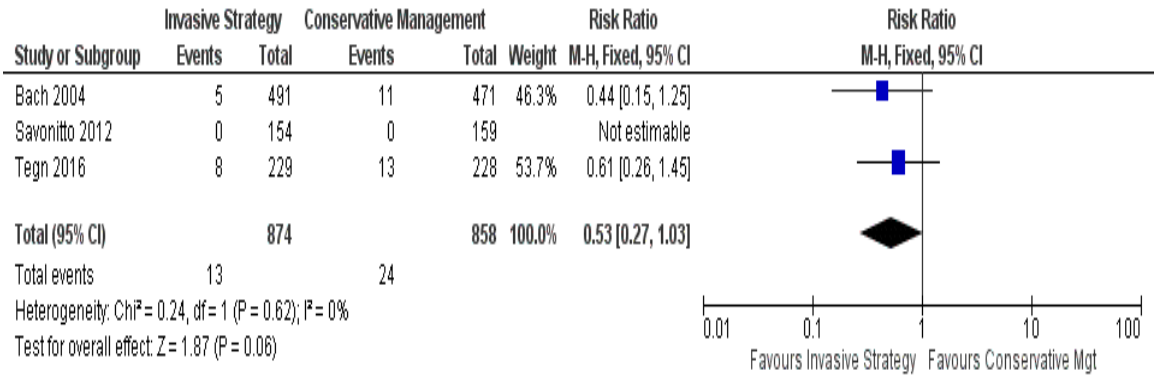

Figure 4. Comparison between invasive and conservative strategy with the outcome of stroke

D. Need for revascularization

In elderly patients with NSTEACS, there were a total of 10 patients among 435 (2%) who needed revascularization in the Invasive Group while there were 34 patients among 441 (8%) in the Conservative Group (Figure 5). The pooled analysis for need for revascularization showed statistically significant benefit with an overall risk ratio of 0.31 (95% CI 0.16 to 0.61) with no significant heterogeneity (p value of 0.0006, I^2 =0%).

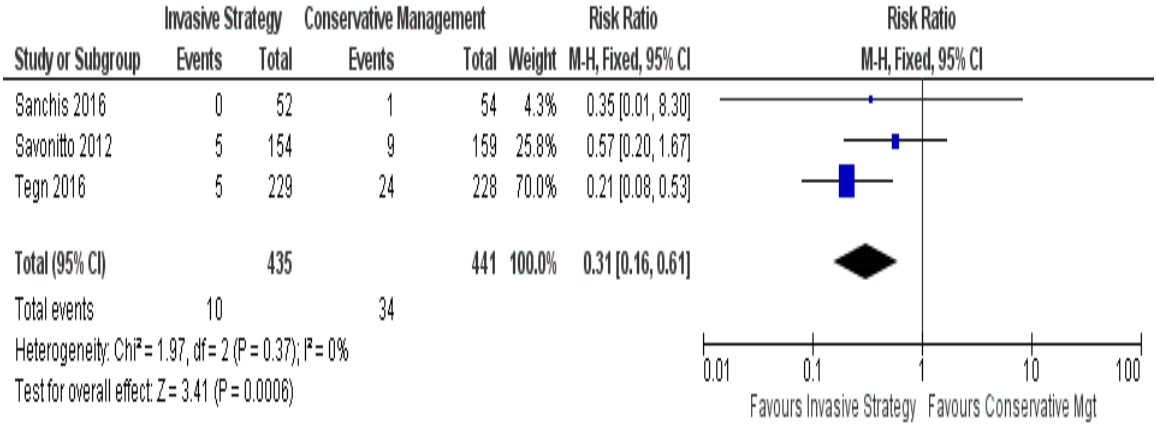

Figure 5. Comparison between invasive and conservative strategy with the outcome of need for revascularization

E. Outcomes for cardiovascular mortality and recurrent angina

Among the five trials, only one trial assessed the outcomes of cardiovascular mortality and recurrent angina.[13] The cardiovascular mortality incidence in the invasive versus the control group was 10% and 11 %, respectively, showing a non-statistically significant benefit of invasive over conservative treatment (RR 0.87, 95% CI, 0.49-1.56, p=0.65). Likewise, an invasive strategy showed a non-statistically significant benefit over conservative treatment in reducing recurrent angina (RR 0.81, 95% CI 0.45–1.46, p=0.49).

VI. DISCUSSION

Meta-analysis of data from the five trials included in this study showed that an early invasive strategy appears to be beneficial in suitable elderly patients $\geq$ 65 years old with NSTEACS. There was significantly less need for revascularization in the invasive strategy group compared to the conservative treatment group. This finding implies that more patients in the conservative group clinically worsened during their course in the ward, requiring revascularization. It is also possible that early anatomic definition of the diseased coronaries may help the attending physician optimize an appropriate evidence-based management of the patient. The studies that evaluated the outcomes of revascularization stated that the indications for revascularization in the conservative group were: positive pre-discharge stress test, poor in-hospital outcomes, recurrent ischemia, reinfarction, malignant ventricular arrhythmias, refractory angina, and heart failure.[12-14] Some patients who subsequently required revascularization could have probably been better off with an early invasive approach.

For the outcomes of death and MI, an invasive strategy showed a statistically significant benefit over conservative treatment but with significant heterogeneity. The possible sources of heterogeneity for the outcomes of death and MI may be the small number of events and sample sizes. In two studies, the elderly population was just a subgroup analysis of the total population.[10-

[11] Hence, the population in the subgroup analysis may not be powered enough to detect the differences in the intervention and outcomes of interest. Furthermore, there were differences in age cutoffs and follow-up period. Two studies had age cutoffs of 75 years[11,13] while the other three studies had age cutoffs of 65, 70, and 80 years.[10,12,14] Possible clinical differences in outcomes may exist in these age brackets of the elderly population. In terms of follow-up periods, two studies had follow-up of 3 years[11,12]; one had follow-up period of 3 months to 3 years[14]; one had follow-up of 1 year[13]; while one had follow-up of 6 months and 1 year[10]. However, despite the heterogeneity, data from these studies clustered on the direction towards benefit favoring invasive over conservative strategy.

In the reduction of stroke, invasive strategy showed benefit over conservative treatment but this was not statistically significant. The outcomes for cardiovascular mortality and recurrent angina were assessed only in one study[13], which showed also a non-statistically significant benefit of invasive strategy over conservative treatment among elderly NSTEACS patients.

Overall, this study does not support the relatively conservative tendency when dealing with elderly patients with NSTEACS in real-life clinical setting. The elderly population is considered a high-risk group wherein more than half the mortality in NSTEACS occur[5] and a more aggressive approach in suitable patients may be more appropriate and beneficial. Among people who die of ischemic heart disease, 83% were >65 years of age.[1] This mortality rate is expected to increase in the forthcoming decades due to improving life expectancy of the elderly. Age is one of the most important predictors of risk in NSTEACS. Each 10-year increase in age results in a 75% increase in hospital mortality in ACS patients.[15] Despite the relatively higher risk in this age group, elderly ACS patients are under-represented in clinical trials such that subjects older than 75 years of age account for less than 10%, and those older than 85 years account for less than 2% of all NSTEACS subjects. [7] This highlights the need for more clinical trials and studies in this age group.

Data from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of

Cardiology/American Heart Association Guidelines) registry showed that NSTEMI patients aged ≥ 65 years who experienced an in-hospital major bleed had a 33% increased risk of 30-day mortality.[16] However, the advancement of equipment and technique has made PCI safer for even very elderly patients (≥ 90 years of age) with high success rates and declining major bleeding risk.[17]

VII. SUMMARY AND CONCLUSION

Results of this meta-analysis suggest some benefits with an early invasive strategy compared to a conservative treatment approach in the management of elderly patients with NSTEACS. There was a significantly lower rate of revascularization in the invasive strategy group compared to the conservative treatment group. A statistically significant benefit favoring invasive strategy was also noted in the reduction of death and myocardial infarction but with significant heterogeneity. These findings do not support the bias against early routine invasive intervention in the elderly group with NSTEACS.

Although an early invasive strategy may be favorable among elderly patients presenting with NSTEACS, the certainty of benefit versus risk still needs to be supported by larger clinical trials and registries with uniform age cutoff for elderly, particularly ≥ 65 years old, to provide high generalizability and statistical power. Current risk scoring systems such as the GRACE (Global Registry of Acute Coronary Events) Score, TIMI (Thrombolysis in Myocardial Infarction) Risk Score, and CRUSADE Bleeding Score are recommended in the initial evaluation of elderly patients presenting with NSTEACS. A special risk scoring may be developed to more accurately identify those who are suitable for an early invasive strategy, with an expected larger outcome and survival benefit.

VIII. ACKNOWLEDGEMENT

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IX. DECLARATION OF CONFLICT OF INTEREST

RRC: member of advisory board or speakers' pool of Servier, Boehringer Ingelheim, Menarini, LRI-Therapharma, Sanofi, UAP Pharma, Unilab; MTR: member of speakers' pool of Novartis, Servier, Astra Zeneca; the rest declare no conflict of interest.

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XI. APPENDIX

APPENDIX A: PubMed Search Strategy

Recent queries in pubmed			
Search	Query	Items found	Time
#100	Search (#42 AND #66 AND #99 AND #20)	322	21:35:50
#99	Search (#92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98)	3218012	21:26:41
#98	Search (#90 OR #91)	50047	21:25:23
#97	Search (#88 OR #89)	4189	21:25:01
#96	Search (#80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89)	344281	21:24:32
#95	Search (#75 OR #76 OR #77)	1549850	21:22:53
#94	Search (#72 OR #73 OR #74)	831057	21:21:59
#93	Search (#69 OR #70 OR #71)	1563389	21:21:19
#92	Search (#67 OR #68)	13679	21:20:30
#91	Search revascularization	50047	21:18:20
#90	Search need for revascularization	3465	21:18:06
#89	Search recurrent chest pain	2911	21:17:56

#88	Search recurrent angina	2673	21:17:31
#87	Search cvd hemorrhage	229	21:17:19
#86	Search cvd bleed	210	21:17:04
#85	Search cvd infarct	2332	21:16:47
#84	Search cerebral bleed	72121	21:16:36
#83	Search cerebral hemorrhage	53180	21:16:24
#82	Search cerebral infarct	49028	21:16:10
#81	Search cerebrovascular event	3648	21:16:00
#80	Search cerebrovascular accident	275080	21:15:40
#79	Search cerebrovascular disease	338376	21:15:16
#78	Search stroke	272396	21:15:01
#77	Search heart attack	229883	21:14:43
#76	Search MI	1344629	21:14:23
#75	Search myocardial infarction	223305	21:14:04
#74	Search cardiac death	720781	21:13:45
#73	Search cardiovascular death	95393	21:13:23
#72	Search cardiovascular mortality	151179	21:13:03
#71	Search death	720781	21:12:35
#70	Search mortality	1044577	21:12:15
#69	Search all-cause mortality	28210	21:11:59
#68	Search MACE	6872	21:11:32
#67	Search major adverse cardiovascular events	9103	21:09:35
#66	Search (#61 OR #62 OR #63 OR #64 OR #65)	6249	21:08:38
#65	Search Invasive Therapy Conservative Therapy	4294	21:07:35
#64	Search Invasive Treatment versus Conservative Treatment	294	21:07:20
#63	Search Invasive Management versus Conservative Management	183	21:07:07
#62	Search Invasive Strategy versus Conservative Strategy	125	21:06:53
#61	Search (#59 AND #60)	2471	21:06:15
#60	Search (#51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58)	125297	21:05:05
#59	Search (#43 OR #44 OR #45 OR #46 OR #49 OR #50)	111701	21:03:38
#58	Search Optimal Medical Therapy	42410	20:59:57
#57	Search Optimal Medical Management	19244	20:59:42
#56	Search Optimal Medical Treatment	48204	20:59:31

#55	Search Optimal Medical Strategy	4920	20:58:27
#54	Search Conservative Therapy	67332	20:58:09
#53	Search Conservative Treatment	56611	20:57:58
#52	Search Conservative Management	66213	20:57:43
#51	Search Conservative Strategy	3336	20:57:30
#50	Search CABG	15615	20:57:16
#49	Search Coronary Artery Bypass Graft	64717	20:56:56
#46	Search PTCA	41266	20:56:38
#45	Search Coronary Angioplasty	46901	20:56:19
#44	Search Percutaneous Coronary Angioplasty	21942	20:55:58
#43	Search Invasive Strategy	9348	20:55:34
#42	Search (#40 AND #41)	52265	20:53:53
#41	Search (#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39)	118669	20:53:22
#40	Search (#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27)	7732231	20:51:38
#39	Search Q-wave myocardial infarction	3366	20:49:40
#38	Search Q-wave MI	757	20:49:29
#37	Search UA	17483	20:49:13
#36	Search unstable angina	17732	20:48:59
#35	Search ACS	63075	20:48:41
#34	Search acute coronary syndrome	25819	20:48:28
#33	Search non-Q wave myocardial infarction	1631	20:48:10
#32	Search non-Q wave MI	400	20:47:57
#31	Search NSTEMI	2072	20:47:39
#30	Search non-st elevation myocardial infarction	8832	20:47:25
#29	Search NSTEACS	228	20:47:10
#28	Search non-st elevation acute coronary syndrome	2893	20:46:51
#27	Search more than or equal to 65 years old	3404034	20:46:33
#26	Search (65 years old and above)	845	20:46:04
#25	Search super centenarian	491	20:45:49
#24	Search centenarian	752696	20:45:34
#23	Search Advanced age	4671906	20:43:19
#22	Search old	898369	20:42:56
#21	Search elderly	4686863	20:42:37

#20	Search (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19)	9528711	20:42:17
#19	Search (Not (animals [mh] NOT human [mh]))	4353823	20:40:33
#18	Search volunteer* [tw]	180971	20:40:13
#17	Search prospectiv* [tw]	709909	20:40:00
#16	Search control* [tw]	4598941	20:39:43
#15	Search prospective studies [mh]	445018	20:39:27
#14	Search follow-up studies [mh]	569279	20:39:03
#13	Search evaluation studies [mh] Schema: all	0	20:38:42
#12	Search evaluation studies [mh]	0	20:38:41
#11	Search comparative study [mh] Schema: all	0	20:38:18
#10	Search comparative study [mh]	0	20:38:18
#9	Search research design [mh:noexp]	92025	20:38:05
#8	Search (((((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw] AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw]))))	1225171	20:37:46
#7	Search ("clinical trial" [tw])	640470	20:37:25
#6	Search clinical trials [mh]	303191	20:36:57
#5	Search clinical trial [pt]	767368	20:36:46
#4	Search single-blind method	39999	20:36:26
#3	Search double-blind method [mh]	140472	20:36:09
#2	Search random allocation [mh]	90997	20:35:54
#1	Search randomized controlled trials [mh]	111611	20:35:19

APPENDIX B.

Sample Data Extraction Template

Trial ID	Extractor	Year of publication
Title		
Authors		
Citation		

Participants

Inclusion criteria:

Exclusion criteria:

398

399 **Intervention**

Treatment group: **Control/Comparison group:**

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401 **Method**

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404 **Quality assessment/ Risk of Bias Table**

Domain	Judgement Low Risk/ High Risk/ Unclear	Support for Judgement/ Description
Method of Random sequence Generation (Selection Bias)		
Method of allocation Concealment (Selection Bias)		
Incomplete Outcome Data/Loss of participants to follow up (Attrition Bias)		
Blinding of Participants and Personnel (Performance Bias)		
Blinding of Outcome Assessment (Detection Bias)		

Selective Reporting/ Intention to treat analysis (Reporting Bias)		
Other Bias		

405

406 **Outcomes**

407

	Outcome Measures (Dichotomous)	*Total* =			
		Intervention group n =		Control group n =	
		Events	total	events	Total
	Primary:				
1					
	Secondary:				

2					
3					

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411 **APPENDIX C.**

412 **Summary of Results of the Five Included Randomized Controlled Trials**

413 **Tegn et al., 2016. After Eighty Study**

414 Invasive versus conservative strategy in patients aged 80 years or older with non-ST-elevation myocardial infarction or

415 unstable angina pectoris (After Eighty study): an open-label randomised controlled trial

416

	Outcome Measures (Dichotomous)	*Total = 457*			
		Intervention group n = 229		Control group n = 228	
		Events	Total	Events	Total
1	All-Cause Mortality	57	-	62	-

2	Cardiovascular Mortality	Not reported		Not reported	
3	Myocardial infarction	39	-	69	-
4	Stroke	8	-	13	-
5	Recurrent angina	Not reported	-	Not reported	-
6	Need for revascularization	5	-	24	-

417

418 **Sanchis et al., 2016.**

419 Randomized comparison between the invasive and conservative strategies in comorbid

420 elderly patients with non-ST elevation myocardial infarction

	Outcome Measures (Dichotomous)	*Total = 106*			
		Intervention group n = 52		Control group n = 54	
		Events	Total	Events	Total
1	All-Cause Mortality	22	-	26	-
2	Cardiovascular Mortality	Not reported	-	Not reported	
3	Myocardial infarction	16	-	11	-
4	Stroke	Not reported	-	Not reported	-
5	Recurrent angina	Not reported	-	Not reported	-
6	Need for revascularization	0	-	1	-

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Savonitto et al., 2012.

Early Aggressive Versus Initially Conservative Treatment in Elderly Patients With Non–ST-Segment Elevation Acute Coronary Syndrome

	Outcome Measures (Dichotomous)	*Total = 313*			
		Intervention group n = 154		Control group n = 159	
		events	Total	Events	Total
1	All-Cause Mortality	19		22	
2	Cardiovascular Mortality	16		17	
3	Myocardial infarction	11		17	
4	Stroke	0		0	
5	Recurrent angina	0		4	
6	Need for revascularization	5		9	

Puymirat et al., 2012. FAST-MI

Use of Invasive Strategy in Non–ST-Segment Elevation Myocardial Infarction Is a Major Determinant of Improved Long-Term Survival

FAST-MI (French Registry of Acute Coronary Syndrome)

	Outcome Measures (Dichotomous) In the Subgroup > 75 years old	*Total = 658*			
		Intervention group n = 412		Control group n = 246	
		Events	Total	Events	Total
1	All-Cause Mortality	119	-	158	-

2	Cardiovascular Mortality	Not reported	-	Not reported	
3	Myocardial infarction	Not reported	-	Not reported	-
4	Stroke	Not reported	-	Not reported	-
5	Recurrent angina	Not reported	-	Not reported	-
6	Need for revascularization	Not reported	-	Not reported	-

Bach et al., 2004.

The Effect of Routine, Early Invasive Management on Outcome for Elderly Patients with Non–ST Segment Elevation Acute Coronary Syndromes

	Outcome Measures (Dichotomous) at 6 Months	*Total = 962*			
		Intervention group n = 491		Control group n = 471	
		Events	Total	Events	Total
1	All-Cause Mortality	5.3 % (25)	-	5.9% (28)	-
2	Cardiovascular Mortality	Not reported	-	Not reported	
3	Myocardial infarction	4.7 % (23)	-	9.6 % (45)	-
4	Stroke	Not reported	-	Not reported	-
5	Recurrent angina	Not reported	-	Not reported	-
6	Need for revascularization	Not reported	-	Not reported	-

APPENDIX D.

Excluded Studies and Reasons for Exclusion

EXCLUDED STUDY	REASON FOR EXCLUSION
Early Invasive Versus Selective Strategy for Non–ST-Segment Elevation Acute Coronary Syndrome: The ICTUS Trial Hoedemaker, MD, Damman, MD, de Winter, MD, et al. Journal of the American College of Cardiology Vol. 69, No. 15, 2017. http://dx.doi.org/10.1016/j.jacc.2017.02.023	> Population: "mean age of the patients in our study was 62 years with relatively few patients older than 80 years" > Outcome: Study presented the number and treatment assignment of patients in the age subgroup > 65 years but did not state the number of outcomes seen per treatment arm.
5-year outcomes in the FRISC-II randomised trial of an invasive versus a non-invasive strategy in non-ST-elevation acute coronary syndrome: a follow-up study Lagerqvist et al. *Lancet* 2006; 368: 998–1004	>Population: Patients were excluded if they were at an advanced age (older than 75 years)
Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial Fox et al. *Lancet 2002;* Vol 360; No. 9349, p 1971-1972. DOI: http://dx.doi.org/10.1016/S0140-6736(02)11864-2	>Population: Did not specify age in the patient selection but described the included population to have a mean age of 62 years >Outcome: Did not report age subgroup results
Elderly patients with myocardial infarction selected for conservative or invasive treatment strategy. Libungan B, Karlsson T, Albertsson P, Herlitz J.	>Population: Included STEMI patients >Method: Retrospective Study

Clin Interv Aging. 2015 Jan 21;10:321-7. doi: 10.2147/CIA.S74012. eCollection 2015.	
Invasive strategy in non-ST elevation acute coronary syndromes: risks and benefits in an elderly population. Lourenço C, Teixeira R, Antonio N, Saraiva F, Baptista R, Jorge E, Monteiro S, Gonçalves F, Monteiro P, Matos V, Calisto J, Faria H, Gonçalves L, Freitas M, Providência LA. Rev Port Cardiol. 2010 Oct;29(10):1451-72. English, Portuguese.	>Method: Observational longitudinal study
Influence of age on use of cardiac catheterization and associated outcomes in patients with non-ST-elevation acute coronary syndromes. Bagnall AJ, Goodman SG, Fox KA, Yan RT, Gore JM, Cheema AN, Huynh T, Chauret D, Fitchett DH, Langer A, Yan AT; Canadian Acute Coronary Syndrome Registry I and II Investigators; Canadian Global Registry of Acute Coronary Events (GRACE/GRACE2) Investigators. Am J Cardiol. 2009 Jun 1;103(11):1530-6. doi: 10.1016/j.amjcard.2009.01.369. Epub 2009 Apr 8.	>Method: Retrospective Study
Effect of an invasive strategy on in-hospital outcome in elderly patients with non-ST-elevation myocardial infarction. Bauer T, Koeth O, Jünger C, Heer T, Wienbergen H, Gitt A, Zahn R, Senges J, Zeymer U; Acute Coronary Syndromes Registry (ACOS) Investigators. Eur Heart J. 2007 Dec;28(23):2873-8. Epub 2007 Nov 2.	>Method: Retrospective Study

Interventional versus conservative treatment in acute non-ST elevation coronary syndrome: time course of patient management and disease events over one year in the RITA 3 trial. Poole-Wilson PA, Pocock SJ, Fox KA, Henderson RA, Wheatley DJ, Chamberlain DA, Shaw TR, Clayton TC; Randomised Intervention Trial of unstable Angina Investigators. Heart. 2006 Oct;92(10):1473-9. Epub 2006 Apr 18.	>Population: Included STEMI patients >Method: Post-Hoc Analysis
Early invasive versus ischaemia-guided strategies in the management of non-Q wave myocardial infarction patients with and without prior myocardial infarction; results of Veterans Affairs Non-Q Wave Infarction Strategies in Hospital (VANQWISH) trial. Heggunje PS, Wade MJ, O'Rourke RA, Kleiger RE, Deedwania PC, Lavori PW, Boden WE; VANQWISH trial investigators. Eur Heart J. 2000 Dec;21(24):2014-25.	>Population and method: Non-Q wave MI patients with prior MI versus patients with first non-Q wave MI

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