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ORIGINAL RESEARCH

Safety of Routine Invasive Versus Selective Invasive Therapy in Women with Non-ST-Elevation Acute Coronary Syndrome

Anthony A. Bavry · Islam Y. Elgendy · Ahmed Mahmoud · Manoj P. Jadhav · Tianyao Huo · Marian C. Limacher · Carl J. Pepine

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ABSTRACT

Introduction: Prior studies suggested that a routine invasive approach in the management of non-ST-elevation acute coronary syndrome (NSTE-ACS) is beneficial in men, but the data are less conclusive in women. One study conducted exclusively in women found that routine invasive therapy was associated with a markedly increased risk of major bleeding. This pilot randomized controlled trial compared the safety of a routine invasive versus a selective invasive strategy among women.

Methods: Women with NSTE-ACS and an additional high-risk characteristic were randomized to a routine invasive versus a selective invasive strategy. The primary outcome was the risk of major bleeding. The secondary outcome was the first occurrence of all-cause death, myocardial infarction, stroke, re-hospitalization for ACS, or major bleeding within 6 months.

Results: Twenty-three women were assigned to routine invasive therapy and 17 to selective invasive therapy. Twenty-seven women (68%) had elevated troponin T (mean 0.33 ng/mL) and/or creatinine kinase-MB (mean 23 ng/mL). The risk of major bleeding was similar with both approaches ($P = 0.99$). At 6 months, the secondary outcome occurred in 9% of the routine invasive group versus 18% of the selective invasive group (risk ratio = 0.49, 95% confidence interval 0.09–2.63, $P = 0.63$).

Conclusion: This pilot study demonstrated that a routine invasive approach is safe in women. There was suggestion of benefit from routine invasive therapy compared with selective invasive therapy. These data could be used to design an appropriately powered trial to determine the optimal management strategy among women with NSTE-ACS.

Keywords: Major bleeding; Myocardial infarction; Non-ST-elevation acute coronary syndrome; Sex differences; Women

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A. A. Bavry (✉)
North Florida/South Georgia Veterans Affairs Health System, Gainesville, FL, USA
e-mail: bavryaa@medicine.ufl.edu; anthony.bavry@va.gov

A. A. Bavry · I. Y. Elgendy · A. Mahmoud · M. P. Jadhav · T. Huo · M. C. Limacher · C. J. Pepine
Department of Medicine, University of Florida, Gainesville, FL, USA

INTRODUCTION

The efficacy and safety of routine invasive versus selective invasive therapy may not apply similarly to women and men with non-ST-elevation acute coronary syndrome (NSTE-ACS). Meta-analyses have documented a reduction in death or myocardial infarction among NSTE-ACS men that undergo routine invasive therapy [1, 2]. However, benefit has been more difficult to detect among NSTE-ACS women who undergo routine invasive therapy. In addition to bleeding differences [3], women appear to be more likely to present with normal or less severe coronary artery disease [4, 5]. The only randomized trial conducted exclusively in women comparing both approaches documented a non-significant increase in death or myocardial infarction among invasively treated women. In fact, invasive therapy was associated with excess mortality at 1 year [6]. In that study, the risk of major bleeding was approximately 9% at 30 days in the routine invasive arm. The patients were treated with either low molecular weight heparin or fondaparinux, which could have contributed to the increased bleeding [7, 8]. The aim of this study was to compare the safety of routine invasive versus conservative strategies in women who are treated with contemporary medical therapy for NSTE-ACS and to determine the adequate sample size for a randomized clinical trial should this approach appear to be safe.

METHODS

Women at least 18 years of age with NSTE-ACS (defined as new-onset chest discomfort at rest or with low levels of activity/or emotion within the preceding 48 h) were eligible if they had an elevated cardiac enzyme (troponin $T \geq 0.03$ ng/mL or creatinine kinase-MB isoenzyme ≥ 5.0 ng/mL). Troponin T was measured by electrochemiluminescence using the Roche Elecsys analyzer, and creatinine kinase-MB was measured by immunoassay using the Roche Cobas analyzer (Roche, Basel, Switzerland). Subjects without elevation in cardiac enzymes were considered eligible if they had an elevated NT-pro-brain natriuretic peptide (NT-proBNP; $\geq$450 pg/mL), ST-segment depression ($\geq$0.5 mm), or thrombolysis in myocardial infarction (TIMI) risk score >2. Exclusion criteria included ST-elevation myocardial infarction, cardiogenic shock, congestive heart failure, hemodynamic instability, use of fibrinolytic therapy in the last 96 h, current bleeding or bleeding disorder within the last 3 months that required transfusion, pregnancy, contraindication to any study medication (heparin, clopidogrel, or glycoprotein IIb/III inhibitor), percutaneous coronary intervention in the last 6 months, or inability to provide written informed consent.

The study protocol was approved by the University of Florida Institutional Review Board. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

Women who provided written informed consent were randomly assigned to a routine invasive versus a selective invasive strategy. Treatment assignment was performed by opening a sealed opaque envelope. The routine invasive group was recommended to undergo coronary angiography within 48 h of hospital admission. Cardiac catheterization was recommended in the selective invasive

group for refractory chest pain, hemodynamic/electrical instability, left ventricular systolic dysfunction, or an abnormal myocardial perfusion stress test; however, patient management decisions were ultimately left to treating physician.

The primary outcome was the risk of major bleeding. Major bleeding was defined as significantly disabling intra-cranial or intra-ocular bleeding, bleeding that required intervention or transfusion, or at least 5 g/dL drop in hemoglobin. The secondary outcome was the first occurrence of all-cause death, myocardial infarction, stroke, re-hospitalization for ACS, or major bleeding within 6 months. Myocardial infarction was defined as an elevation in creatine kinase-MB isoenzyme greater than the upper limit of normal which occurred spontaneously or in the setting of percutaneous coronary intervention. Myocardial infarction in the setting of coronary artery bypass grafting required the presence of new Q-waves [9, 10]. Urgent hospitalization was defined as the need for hospitalization due to an ACS (ST-elevation, non-ST-elevation, or unstable angina) regardless of the treatment delivered (e.g., urgent revascularization versus conservative therapy). Stroke was defined as an ischemic event that caused disabling neurological symptoms that are present for more than 24 h. Urgent target vessel revascularization was defined as recurrent ischemic symptoms that resulted in the need for repeat percutaneous intervention or surgical revascularization. Risk ratio (RR) with 95% confidence interval (CI) for the outcomes was reported. Survival analyses were performed using the Kaplan–Meier method, and the log-rank test was used to compare differences of event-free survival between the two arms. All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC, USA).

RESULTS

Twenty-three women were assigned to routine invasive therapy and 17 to selective invasive therapy. All women had 6-month follow-up (24 women followed to 12 months and 13 women to 24 months). Figure 1 summarizes the study flow diagram. Women were 60 ± 13 years of age, 25% had diabetes, 43% were current smokers, and 68% had a history of hypertension (Table 1). The majority of women received aspirin (98%), beta blockers (88%), and statins (80%). Twenty-seven women (68%) had elevated troponin T (mean 0.33 ng/mL) and/or creatinine kinase-MB (mean 23 ng/mL).

One woman randomized to routine invasive therapy subsequently refused catheterization. In this group, the mean time from randomization to catheterization was 11.7 ± 23.2 h. In the routine invasive group, three women underwent successful percutaneous coronary intervention, while in three women a chronic occlusion was unable to be re-vascularized. In the selective invasive strategy group, catheterization was performed for electrical/hemodynamic instability ($n = 4$), low ejection fraction ($n = 3$), abnormal stress test ($n = 2$), and refractory chest pain ($n = 1$). In the selective invasive group, two women underwent successful percutaneous coronary intervention. Except for one patient in the routine invasive group, catheterization was exclusively performed by femoral artery access.

Only one patient in the routine invasive therapy encountered major bleeding. At 6 months, the composite outcome (intention-to-treat) occurred in 9% of the routine invasive group versus 18% of the selective invasive group (RR = 0.49, 95% CI 0.09–2.63, $P = 0.63$). Additional outcomes are provided in Table 2. At a mean follow-up of 12.5 months, there was a non-significant

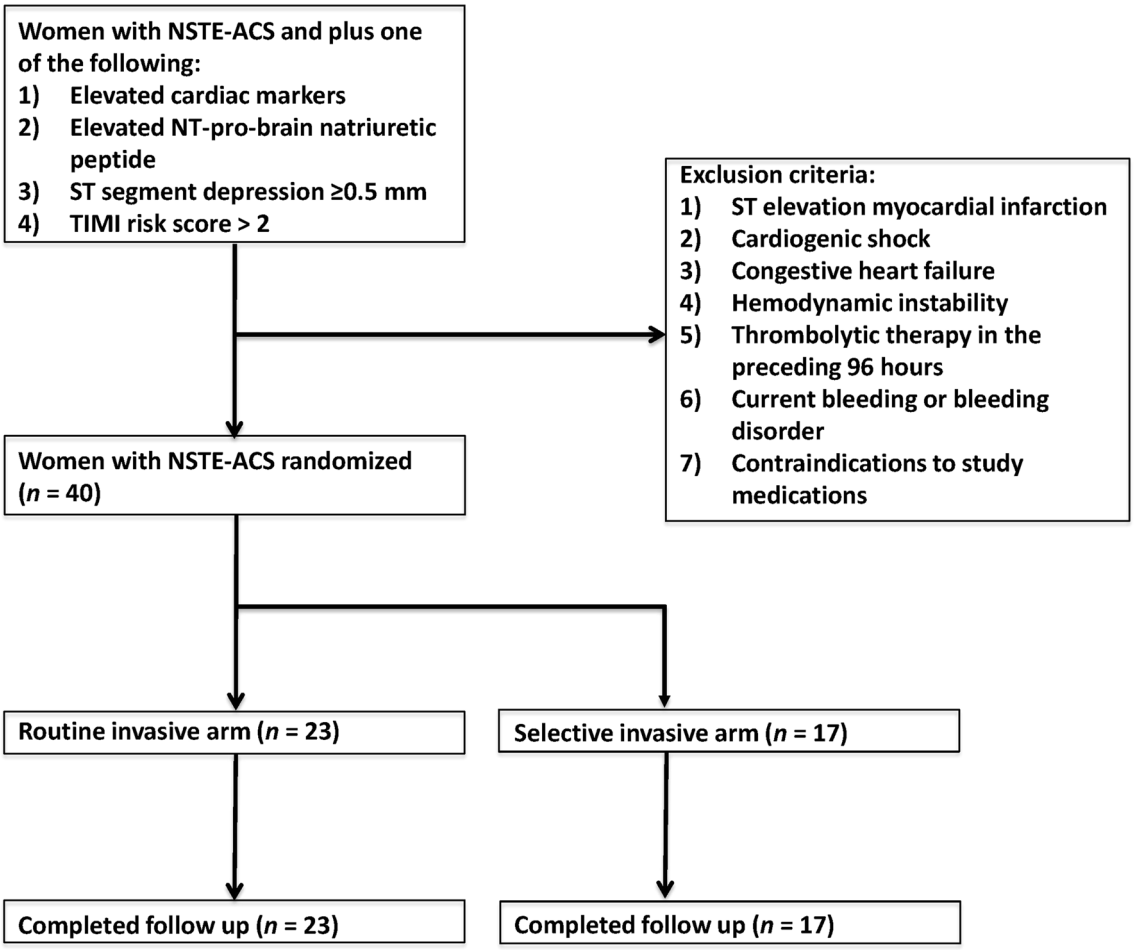

Fig. 1 Study flow diagram. *NSTE-ACS* non-ST-elevation acute coronary syndrome, *TIMI* thrombolysis in myocardial infarction

benefit favoring routine invasive therapy (log-rank $P = 0.11$).

DISCUSSION

Among women with NSTE-ACS, a routine invasive therapy appeared to be safe with no signal for an increase in major bleeding. Although not powered for clinical outcomes, there were numerically fewer adverse cardiovascular events among the routine invasive therapy group. The control arm of our study received selective invasive therapy, which is distinct from conservative therapy. Accordingly, patients underwent monitoring and additional risk stratification during their hospitalization. As a result, many patients crossed over to invasive therapy. However, we do not consider these crossovers to be a limitation, but rather a reality of clinical care.

Although prior meta-analyses had demonstrated the benefits of a routine invasive approach [11, 12], it is important to emphasis that NSTE-ACS clinical trials have shown a remarkable degree of sex bias. In a pooled analysis of ACS trials, women comprised only 25% of the patient population [13]. Furthermore, evidence had shown that

Table 1 Baseline characteristics of the study cohort

Characteristics	Total ($n = 40$)	Routine invasive ($n = 23$)	Selective invasive ($n = 17$)	*P* value
Age, years (mean ± SD)	60 ± 13	58 ± 15	62 ± 10	0.30
Body mass index, kg/m^2 (mean ± SD)	28 ± 9	30 ± 9	26 ± 9	0.19
History of [*n* (%)]				
Diabetes	10 (25)	5 (22)	5 (29)	0.72
Current smoking	17 (43)	10 (43)	7 (41)	>0.99
Hypertension	27 (68)	14 (61)	13 (76)	0.33
Hypercholesterolemia	21 (53)	14 (61)	7 (41)	0.34
Myocardial infarction	7 (18)	6 (26)	1 (6)	0.21
Stroke/transient ischemic attack	6 (15)	5 (22)	1 (6)	0.20
Percutaneous coronary intervention	8 (20)	7 (30)	1 (6)	
Coronary artery bypass grafting	2 (5)	2 (9)	0 (0)	0.50
Medications at randomization [*n* (%)]				
Aspirin	39 (98)	22 (96)	17 (100)	>0.99
Clopidogrel	26 (65)	14 (61)	12 (71)	0.74
ACE inhibitor/ARB	33 (83)	18 (78)	15 (88)	>0.99
Beta blocker	35 (88)	20 (87)	15 (88)	>0.99
Statin	32 (80)	19 (83)	13 (76)	0.70
Insulin	7 (18)	3 (13)	4 (24)	0.43
Laboratory data (mean ± SD)				
Total cholesterol, mg/dL	179 ± 46 ($n = 30$)	173 ± 39 ($n = 18$)	188 ± 55 ($n = 12$)	0.40
Triglycerides, mg/dL	164 ± 102 ($n = 30$)	170 ± 104 ($n = 18$)	154 ± 103 ($n = 12$)	0.66
HDL cholesterol, mg/dL	47 ± 16 ($n = 30$)	48 ± 16 ($n = 18$)	47 ± 16 ($n = 13$)	0.86
LDL cholesterol, mg/dL	113 ± 77 ($n = 29$)	115 ± 93 ($n = 18$)	110 ± 44 ($n = 12$)	0.87
CK-MB, ng/mL[a]	23 ± 19 ($n = 19$)	25 ± 20 ($n = 9$)	21 ± 18 ($n = 10$)	0.67
Troponin T, ng/mL[a]	0.33 ± 0.44 ($n = 25$)	0.38 ± 0.60 ($n = 12$)	0.29 ± 0.20 ($n = 13$)	0.62
NT-proBNP, pg/mL[a]	4636 ± 4775 ($n = 8$)	3913 ± 3716 ($n = 5$)	5841 ± 6980 ($n = 3$)	0.62
Risk scores				
TIMI[b]	3 ± 1	3 ± 1.4	3 ± 1.6	0.45
GRACE[b]	103 ± 29	98 ± 31	110 ± 27	0.21

Table 1 continued

Characteristics	Total ($n = 40$)	Routine invasive ($n = 23$)	Selective invasive ($n = 17$)	*P* value
HAS-BLED[b]	1 ± 1	1 ± 0.99	1 ± 0.94	0.95

ACE angiotensin converting enzyme, *ARB* angiotensin receptor blocker, *CK-MB* creatine kinase-myocardial band, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *NT-proBNP* N-terminal-pro brain natriuretic peptide, *SD* standard deviation

[a] Means obtained among those with CK-MB $\geq$ 5.0 ng/mL, troponin $T \geq 0.03$ ng/mL, and NT-proBNP $\geq$ 450 pg/mL for each category

[b] Median was reported

Table 2 Six-month outcomes

	Routine invasive ($n = 23$) *n* (%)	Selective invasive ($n = 17$) *n* (%)	*P* value
Composite outcome[a]			
Intention to treat	2 (9)	3 (18)	0.63
Actual treatment received	2 (9)	4 (24)	0.26
Other outcomes			
Death	0 (0)	1 (6)[b]	0.43
MI	0 (0)	0 (0)	–
Stroke	0 (0)	1 (6)	0.43
Urgent hospitalization for ACS	1 (4)	2 (12)	0.56
Major bleeding	1 (4)	0 (0)	0.99
Death, MI, stroke, re-hospitalization for ACS	1 (4)	3 (18)	0.29

ACS acute coronary syndrome, *MI* myocardial infarction

[a] Death, MI, re-hospitalization for ACS, stroke, or major bleeding

[b] Death occurred in a patient with acute lymphoblastic leukemia

bleeding events are higher in women undergoing percutaneous coronary interventions compared with men [14, 15]. Therefore, this pilot study aimed to address the question whether a routine invasive approach would be safe. Although the OASIS-5 sub-study had addressed this same question, the bleeding events in that study were remarkably high which could have been attributed to the study design [6].

Although we attempted to enroll high-risk women, the proportion of women who underwent revascularization was low (i.e., <20%). Approximately one-fifth of women had a chronic total occlusion, which is similar to previous findings [16]. While 68% of our study participants were eligible due to elevated cardiac enzymes, the remainder met other eligibility characteristics which might not adequately risk-stratified patients. However,

the median TIMI risk score was 3 and in the TACTICS-TIMI 18 trial, intermediate- to high-risk patients (score ≥ 3) benefited from invasive therapy [17]. Current guidelines recommend routine invasive therapy for high-risk women (i.e., elevated troponin); however, routine invasive therapy is less favorable in low-risk NSTE-ACS women [18]. Based on our observed 6-month event rate of 18% in the selective invasive arm, we estimate that 3454 patients would be needed to detect a 20% relative difference between treatment arms with 80% power.

CONCLUSION

This study demonstrates that a routine invasive approach is safe in women. There was suggestion of benefit from routine invasive therapy compared with selective invasive therapy. These data could be used to design an appropriately powered trial to determine the optimal management strategy among women with NSTE-ACS.

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Compliance with Ethics Guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

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