Nadroparin and Percutaneous Transluminal Coronary Angioplasty in Elderly Thais with Unstable Angina

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ABSTRACT

Objective: Unstable angina (UA) is one of the leading problems in healthcare management in developing countries where facilities of catheterization laboratory are scarce and well-trained operators who are able to manage acute coronary syndrome often unavailable. In this scenario, strategy to arrive at optimal management to stabilize the condition medically is always a controversy, concerning the optimal management strategy during medical stabilization at places with inadequate catheterization laboratory facilities and a lack of well-trained operators. Furthermore, the choices of medical and invasive management, including the use of percutaneous transluminal coronary angioplasty (PTCA) are still debatable. Curious by the challenge, we launch this prospective randomized controlled study to compare the efficacy of nadroparin with percutaneous transluminal coronary angioplasty (PTCA) in elderly patients with UA or non ST-elevation myocardial infarction (NSTEMI).

Methods: Ninety-three elderly patients with UA, whose clinical manifestations were classified according to Braunwald's classification, were recruited. All patients underwent coronary angiography within 96 hours after hospitalization; those who had angiographic coronary arterial stenosis that was feasible for PTCA were randomized to receive either nadroparin 7,500 IU subcutaneously twice daily for 5 days or PTCA. All clinical events in hospital and post-discharge up to 12 months, including death, composite end point [myocardial infarction (MI), recurrent angina/or ischemia], re-intervention (either PTCA or coronary artery bypass surgery) and rehospitalization, were recorded.

Results: Only Forty-six patients were randomized equally into NAD group (n =23) and PTCA group (n =23). There were no statistically significant differences between NAD vs. PTCA regarding their baseline clinical characteristics, ECG, number of diseased vessels involved and outcomes (death and MI). The composite end point occurred more frequently in the NAD group [(34.5% vs. 4.3%); p = 0.01]. After a 12-month follow-up there was no difference in death rate or MI between the two groups but there was a clinically significant difference with regard to post-discharge outcomes in the NAD group, i.e, higher recurrent angina in NAD *vs.* PTCA (43.5% *vs.* 23.7%; p = 0.012), requiring additional PTCA (39.1% *vs.* 21.7%; p = 0.012), rehospitalization (47.8% vs. 30.4%; p = 0.015) and composite endpoint (47.8% *vs.* 30.4%; p = 0.015).

Conclusions: PTCA achieve less composite endpoint than conservative management while nadroparin was easy to administer, but one-third of the patients still experienced recurrent angina or ischemia. PTCA is another option and could be performed safely, resulting in a less recurrent angina and shorter hospital stay. It is suggested that in the elderly with UA, nadroparin may be considered is the initial optimal management where PTCA facility is not available; those with recurrent angina symptoms should be referred afterwards for PTCA.

Keywords: Unstable angina; Percutaneous transluminal coronary angioplasty; Heparin; Nadroparin; Conservative treatment; Elderly

Siriraj Med J 2005; 57:313-318

The current treatment of acute coronary syndrome (ACS) has changed since the introduction of new drugs such as low-molecular weight heparin (LMWH) and glycoprotein IIb/IIIa receptor blocker (GPIIa/IIIb).[1,2] Conventional treatments associated with pathophysiology include aspirin, nitrates, β-blockers, calcium channel blockers and unfractionated heparin (UFH). Gurfinkel et al.[3] reported that nadroparin had the same efficacy as UFH in patients with unstable angina (UA) or non-ST segment elevation myocardial infarction (NSTEMI). Worldwide, there is a large variation in the outcome (death, myocardial infarction and recurrent myocardial infarction) in patients with UA/NSTEMI. Clinical practice is influenced by a variety of factors including the incidence of coronary heart disease in the local population, the availability of resources and the current perception of available treatments within the medical community. A lack of catheterization laboratory facilities creates a non-uniform treatment strategy. The decision to treat is based on the resources available to the physician. The aim of this study was to assess the impact of different in-hospital management strategies between the use of percutaneous transluminal coronary angioplasty (PTCA) and the use of LMWH or nadroparin (NAD) treatment in elderly patients with unstable angina /NSTEMI.

MATERIALS AND METHODS

Patient populations

Patients were recruited into the study from October 1, 1997 to September 30, 1998. Inclusion criteria were: 1) age 60-80 years old; 2) angina at rest within 24 hours of onset; 3) no evidence of persistent ST-segment elevation; 4) left ventricular ejection fraction >40% (from echocardio graphy); 5) no bleeding diathesis; 6) serum creatinine <2.5 mg/dl; and 7) patients written informed consent form [m3]to revascularization if necessary. Exclusion criteria were: 1) cardiogenic shock; 2) underlying medical illness that may affect the clinical outcome such as hepatic or renal failure or advanced cancer; and 3) lesions unsuitable for angioplasty such as left main stenosis, a severely calcified lesion or stenosis of major side-branches larger than 2.5 mm in diameter. Enrolled patients were required to undergo thorough physical examinations, laboratory investigations and were then classified according to Braunwalds classification for unstable angina. Laboratory investigation included ECG, serum analysis of blood urea nitrogen, creatinine, and creatine kinase-MB (CKMB). An echocardiography was performed on all patients. ECG at presentation was classified as dynamic ST-T elevation (non persistent), ST-T depression, T-wave inversion or normal. Patients were classified according to the likelihood of short-term risk of death or myocardial infarction. Patients who agreed to join the study were treated with 325 mg of aspirin daily and other drugs as needed. Written informed consents were obtained from all patients. The Ethics Committee on Human Rights involving Human Research of the Faculty of Medicine, Siriraj Hospital, has approved the study protocol.

Study design and treatment protocol (Fig 1)

This study was a prospective randomized, controlled trial among elderly patients. A coronary angiography was performed on all enrolled elderly patients within 96 hours of admission. The number of target vessels involved was counted. The lesions were analyzed as the culprits in the presence of thrombus and the TIMI flow grade 0-2 (Thrombolysis in Myocardial Infarction). Quantitative coronary analysis was measured for coronary diameter, using Philips package software analysis version 2.0. Disease stenosis was defined if >60%. The lesion morphology was assessed for the feasibility of PTCA. Patients were randomized to receive either PTCA or NAD. In the PTCA group, the most likely culprit lesion was attempted first. If there was another lesion, it might be treated according to the operator's decision; provisional stent implantation was allowed according to the result of angioplasty. In the NAD group, nadroparin (Sanofi Synthelabo) 7,500 IU was administered subcutaneously every 12 hours for 5 consecutive days.

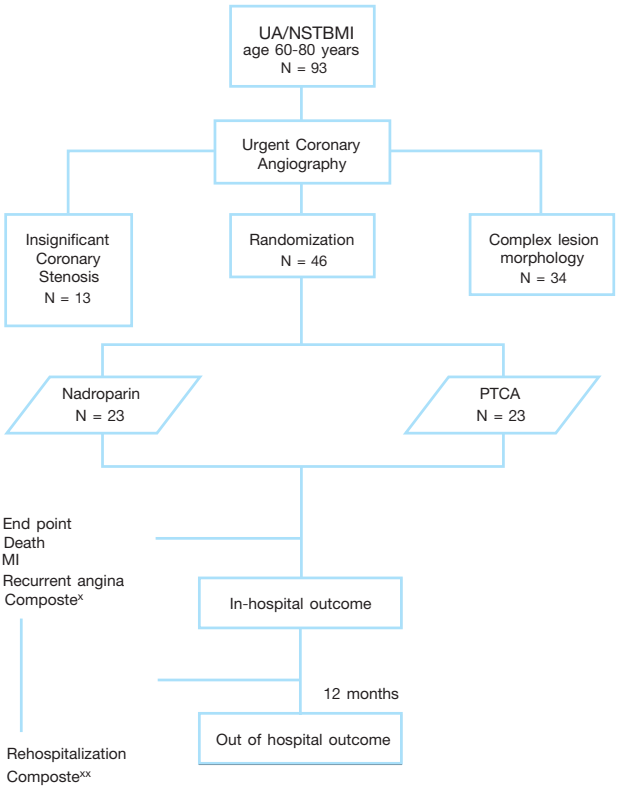

Fig 1. Design of the study randomized to two treatment groups.

End Points

The primary outcome of the trial was the composite end point of death, myocardial infarction (MI), or recurrent angina during admission. The secondary outcome was the composite end point of death or MI; the number of re-intervention recurrent angina that required rehospitalization was also recorded at a 12-month follow-up.

Definitions

Death was defined as any death, regardless of its cause. Myocardial infarction was defined as: 1) a total elevation of creatinine kinase MB more than twice the upper normal limit or ST-segment elevation in at least two leads. Recurrent angina was defined as angina at rest with duration longer than ten minutes that was associated with a new ST-segment shift (elevation or depression) of more than 0.1 mV, or with T-wave inversions in two contiguous electrocardiographic leads, or angina after hospital discharge that resulted in readmission.

Follow-up

The patients were followed from admission to the in-hospital end point. After discharge, the patients were followed for one month and then every three months for a

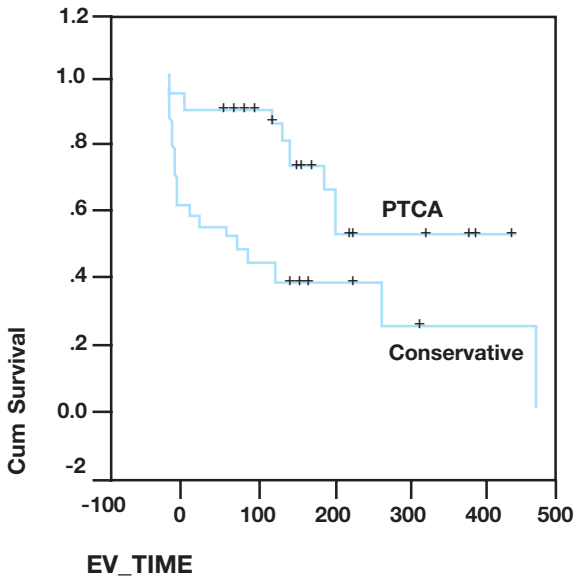

Fig 2. Cumulative Kaplan-Meier survival curve of triple end points.

TABLE 1. Baseline characteristics of study patients according to treatment group.

	Randomization		Non-Randomization
	Nadroparin (n=23)	PTCA (n=23)	Intent-to-treat (n=47)
Age (yr) mean (SD)	69.36 (5.7)	66.94 (5.3)	67.27 (6.4)
LV ejection fraction (%)	61.29 (11.3)	61.57 (10.9)	60.09 (12.9)
Female sex (%)	13 (56.5)	19 (83.6)	31 (64.0)
Risk factors			
Diabetes (%)	9 (39.1)	7 (30.4)	23 (48.9)
Hypertension (%)	15 (65.2)	12 (52.2)	33 (70.2)
Hypercholesterolemia (%)	10 (43.5)	14 (60.9)	22 (46.8)
History of Smoking (%)	8 (34.8)	4 (17.4)	12 (25.5)
Family history of CAD (%)	2 (8.7)	0	5 (10.6)
Prior cardiac history			
Prior PTCA (%)	1 (4.3)	2 (8.7)	1 (2.1)
Prior CABG (%)	0	0	1 (2.1)
Prior history of MI (%)	3 (13.0)	3 (13.0)	7 (14.9)
Presence of heart failure (%)	4 (17.4)	2 (8.7)	12 (25.5)
Prior CPR (%)	1 (4.3)	0	0
Electrocardiographic changes			
ST-segment elevation (transient) (%)	1(4.3)	3 (13)	5(10.6)
ST-segment depression (%)	15 (65.2)	9 (39.1)	24 (48.9)
T-wave inversion (%)	5 (21.7)	9 (39.1)	9 (19.1)
BBB (LBB or RBB block) (%)	1 (4.3)	1 (4.3)	2 (4.3)
Normal (%)	1 (4.3)	1 (4.3)	8 (17.0)

TABLE 2. Baseline characteristics of patients according to treatment group.

	Nadroparin (n=23)	PTCA (n=23)	p value
Severity of angina			
Class I	3 (13.0%)	2 (8.7%)	
Class II	9 (39.1%)	10 (43.5%)	NS
Class III	11 (47.8%)	11 (47.8%)	
Type of angina			
Class A	1 (4.3%)	0	
Class B	19 (82.6%)	21 (91.3%)	NS
Class C	3 (13.0%)	2 (8.7%)	
Intensity of treatment			
Class a	7 (30.4%)	6 (26.1%)	
Class b	14 (60.9%)	12 (52.2%)	NS
Class c	2 (8.7%)	5 (21.7%)	
Clinical presentation			
Rest angina	14 (60.9%)	18 (78.3%)	
New onset angina	4 (17.4%)	1 (4.3%)	NS
Crescendo angina	3 (13.0%)	2 (8.7%)	
Post MI angina	2 (8.7%)	2 (8.7%)	0.29
CAD likelihood			
High	18 (78.3%)	19 (82.6%)	0.71
Intermediate	5 (21.7%)	4 (17.4%)	
Low	0	0	
Short term risk			
High	11 (47.8%)	13 (56.5%)	0.56
Intermediate	12 (52.2%)	10 (43.5%)	
Low	0	0	

period of twelve months. Medical information was recorded in a case-record form designed prior to the study.

Statistical analysis

Dichotomous variables were analyzed by a non-parametric test using chi-square test and the Kruskal-Wallis One-way analysis of variance for a set of data containing more than two groups. Statistical significance was taken when p-value < 0.05.

RESULTS

Ninety-three patients were enrolled; 46 patients had suitable lesion morphology for PTCA and were randomized into two groups. Forty-seven patients were excluded from the study but were analyzed for symptoms. Baseline characteristics were similar in both groups (Table 1). There were no differences in any baseline variables between the two treatment groups.

Clinical presentations

Sixty-six patients (70.9%) had angina at rest within 24 hours of entry to the study. Ten patients (10.8%) experienced a first episode of angina, eleven patients (11.8%) had crescendo angina within the last two months, and seven patients (7.5%) had post- MI angina. Seventy-nine patients (84.9%) had no precipitating cause for the development of unstable angina (Class B); 50 patients (53.8%) were classified as high-risk subgroups for death or MI. Twenty-three patients were ran domized to receive PTCA (n=23) and the other 23 patients received conservative treatment (nadroparin). The characteristics of the angina, the likelihood for coronary arterial disease and the short-term risk for subsequent death or myocardial infarction, according to the treatment group, are shown in Table 2. Our study has higher incidences of angina severity, Braunwald's Class B angina, more rest angina, a high likelihood for coronary artery disease and a high short-term risk for death or myocardial infarction.

Coronary Angiography (n = 97)

Thirteen patients (13.9%) had insignificant coronary stenosis; eight (8.6%) had left main coronary stenosis and twenty-six patients

TABLE 3. Distribution of number of vessel stenosis according to treatment group.

	Nadroparin (n=23)	PTCA (n=23)	p value
Single vessel disease	8 (34.7%)	10 (43.5%)	
Double vessel disease	10 (43.5%)	9 (39.1%)	0.45
Triple vessel disease	5 (21.7%)	4 (17.4%)	

TABLE 4. Outcome of events during admission.

	Nadroparin (n=23)	PTCA (n=23)	Risk Reduction	p value
Composite	8 (34.5%)	1 (4.3%)	0.87	0.01*
Death	0	0	-	
MI	0	1 (4.3%)	-	0.32
Recurrent angina	8 (34.8%)	0	-	0.02*
Total revascularization	7 (30.4%)	1 (4.3%)	0.7	0.01*
Additional PTCA	5 (21.7%)	1 (4.3%)	0.20	0.07
CABS	2 (8.7%)	0	-	0.15
Days of hospitalization	10.5 ± 6.1	7.1 ± 4.9	-	0.001*

* statistical significance

(27.9%) had unfavorable coronary morphology. After randomization, an equal distribution of the number of stenosed vessels was found in both treatment groups (Table 3).

In-hospital outcomes

PTCA arm: Target lesions for revascularization (TLR) were performed on 31 lesions (1.34 TLR per patient). Fifteen patients had complete revascularization. The overall success rate of PTCA was 95.6%. The incidence of the composite end point (death, myocardial infarction or recurrent angina) is shown in Table 4. Acute MI occurred in one patient in the PTCA group due to acute vessel closure following angioplasty. Coronary stent was unable to be manipulated across the calcified vessel.

Nadroparin arm (or conservative): Eight patients (34.5%) had recurrent angina. Five patients (21.7%) finally underwent coronary angioplasty and two (8.7%) underwent coronary artery bypass surgery (CABS) compared to only one in the PTCA group (4.3%) who underwent repeated angioplasty. Hospitalization was longer in the nadroparin than in the PTCA group (10.5 ± 6.1 vs. 7.1 ± 4.9 days; p = 0.001). The in-hospital mortality was not different between the two groups (p = 0.32).

TABLE 5. Long-term outcomes during follow-up.

	Nadroparin (n=23)	PTCA (n=23)	Risk Reduction	p value
Composite	11 (47.8%)	7 (30.4%)	0.64	0.015*
Death	0	0	-	1.00
MI	0	1 (4.3%)	-	0.32
Recurrent angina	10 (43.5%)	5 (21.7%)	0.5	0.012*
Re-hospitalization	11 (47.8%)	7 (30.4%)	0.64	0.015*
Total revascularization	10 (43.5%)	7 (30.4%)	0.7	0.012*
Additional PTCA	9 (39.1%)	5 (21.7%)	0.56	0.012*
CABS	1 (4.3%)	2 (8.7%)	2.02	0.55

* statistical significance

Long-Term Outcomes

Clinical evaluation was performed on day 30 and every 3 months for 12 months, unless there was rehospitalization due to an ischemic event. These outcomes are shown in Table 5. Patients in the PTCA group had less recurrent angina than those in the NAD group (21.7 % vs. 43.5 %; p = 0.012) and underwent fewer coronary procedures (21.7 % vs. 39.1 %; p = 0.012). Rehospitalization and new by pass surgery during the 12-month follow-up were not different between the two treatment groups. Cumulative event (triple end points) survival with time between two treatment groups was demonstrated. A significant separation line was shown since the early period of follow-up to day 100 demonstrated that patients in the conservative group met one of the triple end points earlier than the PTCA group. After day 300 the separation tended to reach a plateau due to the needs of re-intervention in the conservative group.

DISCUSSION

To our knowledge, this is the first study that evaluates the efficacy of two different strategies comparing nadroparin with balloon angioplasty. In our study, all patients underwent coronary angiography before randomization; those who were enrolled in the PTCA arm received balloon angioplasty treatment. Therefore, the most severe diseases, such as left main or severe triple vessel stenosis or those with normal coronary angiography or insignificant coronary stenosis were excluded. In contrast, previous studies such as TIMI IIIB and VANQWISH[4,5] compared the invasive approach (coronary angiography with or without revas cularization) with the conservative treatment (no coronary angiography unless indicated) and may have included those with insignificant coronary disease. We compared the two different strategies without other confounding factors. Another factor was that the enrolled patients were elderly, with a well-preserved left ventricular ejection fraction (LVEF) >40 % (mean 61.2%) and the use of an anticoagulating agent (nadroparin). The main primary endpoint (death, MI, recurrent ischemia) in our study favors the PTCA strategy over the NAD (4.3% vs. 34.5%; p =0.01). However, there was no difference in the rate of death or MI between the two strategies, but it was slightly higher than reported by TIMI-3B at 42 days and one year.[4] Recurrent ischemia and the need for a crossover to PTCA in the NAD group was higher than what reported by others.[3] The primary and secondary outcomes were fewer in the PTCA group and were compa-

rable to FRISC-II.[6] However, during the 12-month follow-up, there were significant differences in the composite end points, and tended to reveal a higher incidence of readmission in the NAD group.

In our study, the question was whether the results of these randomized trials could be replicated in a community setting. It is unlikely that PTCA could be performed in community hospitals as effectively as in high-volume centers. Indeed, the angioplasty success rate in our study (96.5%) was substantially equivalent to that reported by TIMI IIIB investigators. One potential advantage of interventional treatment is the possibility of reducing the rates of readmission and subsequent revascularization procedures by performing those during the index admission. In the NAD group, the patients underwent more procedures after discharge (43.5%). Unfortunately, those treated initially with PTCA had a rather high reintervention rate (30.4%). This is due to high clinical restenosis in the PTCA group, which required repeated PTCA, explained by less use of coronary stent in conjunction with PTCA and GPIIb/IIIa inhibitors. The other investigators in EPIC[7] PURSUIT[8] and TACTICS-TIMI 18[9] demonstrated an early and durable benefit of such therapy. Reductions in death or MI were apparent in the context of both PTCA and NAD treatment approaches without statistical significance. Study limitation

The number of patients enrolled was probably too small to demonstrate the effects such as the rate of death and MI of these two-treatment groups. The lower rate of implanted coronary stent during PTCA might affect the high rate of restenosis post PTCA and recurrent ischemia requiring a repeat of PTCA afterwards.

CONCLUSION

PTCA is as safe and effective as nadroparin in the treatment of elderly patients with UA/NSTEMI. The composite endpoint was lower in the PTCA group, despite no difference in short- or long-term mortality. The rate of subsequent procedures and cumulative readmission tended to be higher in the nadroparin group. However, cumulative costs tended to be higher in the PTCA group. A combination of PTCA with nadroparin might potentiate a better outcome in practice. In the future, the combination regimen of the GPIIb/IIIa inhibitor, along with the use of coronary stent plus heparin and an invasive approach, is likely to become the new therapy in this clinical setting.

Nevertheless, it is suggested that where a PTCA facility is not available for our elderly patients with UA, nadroparin may be the initial optimal treatment, and those with recurrent angina symptoms should be later referred for PTCA.

ACKNOWLEDGEMENTS

This study was supported by the National Research Council of Thailand. We are also grateful to the medical staff of Her Majesty's Cardiac Center, Siriraj Hospital, for their contributions in PTCA treatment.

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บทคัดย่อ

นาโดรพารินและการขยายหลอดเลือดหัวใจด้วยบอลลูนในผู้สูงอายุเจ็บเค้นอกแปรผัน

ดำรัส ตรีสุโกศล พ.บ., อดทน ศรียุทธศักดิ์ พ.บ., ประดิษฐ์ ปัญจวีณิน พ.บ., เธวัตร พันธุ์กิ่งทองคำ พ.บ.

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วัตถุประสงค์: เนื่องจากประชากรสูงวัยมีจำนวนเพิ่มขึ้น และมักจะมาพบแพทย์ด้วยโรคเจ็บเค้นอกแปรผัน ซึ่งมีโอกาสเกิดโรคกล้ามเนื้อหัวใจตายเฉียบพลันหรือเสียชีวิตได้บ่อย การรักษามาตรฐานได้แก่การรักษาด้วยยาโดยเฉพาะการให้ยา หรือการรักษาชนิดคุกคาม ซึ่งยังเป็นข้อถกเถียงและสำหรับคนไทยยังไม่มีแนวทางการรักษาที่เหมาะสมในสถานบริการที่ขาดทั้งเครื่องมือและบุคลากรที่ชำนาญในการขยายหลอดเลือดหัวใจด้วยบอลลูน เพื่อเปรียบเทียบผลการรักษาการเจ็บเค้นอกแปรผันด้วยยานาโดรพาริน (NAD) กับการขยายหลอดเลือดหัวใจด้วย (PTCA) ในผู้ป่วยสูงวัย

วิธีการศึกษา: เป็นการศึกษาแบบสุ่ม โดยมีผู้ป่วยสูงวัยอายุ 60-80 ปี 93 รายที่มีอาการเจ็บเค้นอกแปรผัน มีค่าครีเอตินีน ต่ำกว่า 2.5 มก./ดล. และค่าการบีบตัวของกล้ามเนื้อหัวใจ > 40% ทุกรายจะได้รับการตรวจสวนหลอดเลือดหัวใจภายใน 96 ชม. แรกภายหลังรับไว้รักษาตัวในรพ. ผู้ป่วยที่มีร่องรอยโรคหลอดเลือดหัวใจที่ตีบรุนแรงและเหมาะสมสำหรับการรักษาด้วย PTCA จำนวน 46 รายได้รับการจำแนกโดยการสุ่มเป็นกลุ่มที่ได้รับยา Nadropain (NAD) ขนาด 7,500 ยูนิต ฉีดเข้าใต้ผิวหนังวันละ 2 ครั้ง นาน 5 วัน 23 ราย และกลุ่มที่ได้รับการรักษาด้วย PTCA 23 ราย ติดตามผลการรักษาขณะผู้ป่วยอยู่ในรพ. และหลังจำหน่ายกลับบ้านนาน 12 เดือน ประเมินผลการรักษารวมขณะอยู่ในร.พ. ได้แก่อุบัติการที่ผู้ป่วยเสียชีวิต, เกิดกล้ามเนื้อหัวใจตายเฉียบพลันและอาการเจ็บเค้นอกซ้ำ และผลการรักษาขณะติดตาม 12 เดือน ได้แก่อุบัติการที่ผู้ป่วยเสียชีวิต, เกิดกล้ามเนื้อหัวใจตายเฉียบพลัน, เจ็บหน้าอกซ้ำ การที่ผู้ป่วยได้รับการทำ PTCA ซ้ำหรือการผ่าตัดต่อหลอดเลือดหัวใจและอัตราการกลับเข้ารักษาซ้ำในรพ.

ผลการศึกษา: กลุ่ม NAD เทียบกับ PTCA ผลการรักษาพบว่าในรพ. อัตราตาย และเกิดกล้ามเนื้อหัวใจตายเฉียบพลันทั้ง 2 กลุ่มไม่ต่างกันแต่เกิดเจ็บเค้นอกซ้ำในกลุ่ม NAD (34.8% vs. 0%, p = 0.02) ต้องเปลี่ยนมารักษาโดยวิธี PTCA 21.7% และผลการรักษารวม (34.5% vs. 4.3%, p = 0.01) บ่อยกว่ากลุ่ม PTCA เมื่อติดตามผู้ป่วยหลังออกจาก ร.พ. ไม่มีผู้ป่วยเสียชีวิต แต่กลุ่ม NAD เกิดเจ็บเค้นอกซ้ำ (43.5% vs. 23.7%, p = 0.012); ต้องทำ PTCA ซ้ำ (39.1% vs. 21.7%, p = 0.012); รักษาในโรงพยาบาลซ้ำ (47.8% vs. 30.4%, p = 0.015) และผลการรักษารวม (47.8% vs. 30.4%, p = 0.015) บ่อยกว่ากลุ่ม PTCA

สรุป: PTCA ให้ผลการรักษาที่มีประสิทธิภาพสูงกว่านาโดรพาริน ในขณะที่การใช้ยานาโดรพาริน สะดวก ปลอดภัยและได้ผลดีในระยะสั้นไม่ต่างจาก PTCA แต่ผู้ป่วย 1 ใน 3 เกิดเจ็บเค้นอกซ้ำได้บ่อยกว่ากลุ่ม PTCA ทั้งนี้ไม่พบความแตกต่างในอัตราการตายหรือการเกิด MI ตลอดการรักษาและเมื่อติดตาม 12 เดือน คณะผู้วิจัยเชื่อว่าผู้สูงอายุที่มีการเจ็บเค้นอกแปรผัน การรักษาในช่วงแรกด้วยนาโดรพาริน ยังเป็นทางเลือกหนึ่งสำหรับสถานบริการที่ไม่สามารถทำ PTCA ได้ และผู้ที่เกิดอาการเจ็บเค้นอกซ้ำหลังได้ยาควรได้รับการส่งต่อเพื่อรับการทำ PTCA ต่อไป