

Multivessel Stenting versus Culprit-Only Stenting in Multivessel Coronary Artery Disease Patients Presented with Non-ST-Segment Elevation Acute Coronary Syndrome (NSTEMI-ACS)

Abstract

Background: Multivessel disease (MVD) is noted in about half of patients with NSTEMI-ACS. It is associated with worse outcome.

Objectives: In the current study, we compared multivessel PCI versus culprit-only PCI in patients presented with NSTEMI-ACS who have MVD.

Methods: This prospective, controlled study included 50 consecutive patients with NSTEMI-ACS. All patients had multi-vessel CAD with $\geq 70\%$ diameter stenosis estimated visually or using quantitative coronary angiography (QCA) on coronary angiography. 50% of patients underwent culprit only PCI, while 50% had total revascularization. Thirty days adverse cardiovascular events were reported in both groups.

Results: No mortality was reported in either group. Re-hospitalization due to ACS was reported in 16% of patients (20% versus 12% in culprit only and total revascularization patients respectively, $p=0.15$). Target or new target revascularization was reported in 6% (12% versus 0% in culprit only and total revascularization patients respectively, $p=0.03$). Re-infarction was reported in 4% of all patients, all of them were from culprit only PCI patients, $p=0.14$.

Conclusion: Total revascularization PCI is feasible, efficient and safe compared with culprit vessel PCI in patients with MVD presenting with NSTEMI-ACS.

Keywords: NSTEMI-ACS; Culprit artery; Total revascularization

Research Article

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Abbreviations: NSTEMI-ACS: Non-ST-Segment Elevation Acute Coronary Syndrome; MVD: Multivessel disease; NSTEMI: Non-ST-Segment Elevation Myocardial Infarction; PCI: Percutaneous Coronary Intervention; MVR: Multivessel Revascularization; CAD: Coronary Artery Disease; QCA: Quantitative Coronary Angiography

Introduction

Atherosclerotic Coronary artery disease (CAD) is a diffuse process and, often, patients presenting with unstable angina or non-ST-segment elevation myocardial infarction (NSTEMI) have multiple lesions that may be suitable for percutaneous coronary intervention (PCI) [1]. In the era of contemporary medical therapy, it is not clear whether intervening on stable chronic nonculprit lesions in patients with NSTEMI-ACS can prevent major adverse cardiovascular events. In addition, multivessel stenting in this setting could potentially be associated with greater dye load and periprocedural myocardial infarction (MI) secondary to side branch closure and distal embolization [2]. Multivessel disease (MVD) is noted in about half of patients with NSTEMI-ACS [3]. It is associated with increased mortality after MI [4]. In the Framingham and Fast Revascularization During Instability in Coronary Artery Disease (FRISC) II trial, one of the landmark studies that changed the NSTEMI strategy toward an early

invasive strategy, revascularization was recommended in any artery with $>70\%$ stenosis [5]. However, it is not clear whether multivessel percutaneous coronary intervention (PCI) beyond the culprit lesion in patients with NSTEMI-ACS and MVD can improve long-term prognosis. Few studies have compared long-term outcome of multivessel revascularization (MVR) and single-vessel revascularization (SVR) in patients with NSTEMI-ACS and MVD undergoing PCI [6]. Moreover, these studies were conducted in the era of bare-metal stents. In the current study, we compared multivessel PCI versus culprit-only PCI in patients presented with NSTEMI-ACS who have MVD.

Patients and Methods

Study Design

This prospective, controlled, phase II study included 50 consecutive patients with NSTEMI-ACS who were admitted to the coronary care unit (CCU) at the National heart institute, during the period from December 2011 to February 2013. The study aimed to test the safety and efficacy of multivessel PCI compared with culprit-only PCI in patients with NSTEMI-ACS. All patients signed an informed consent and the study was approved by local ethics committee. Key inclusion criteria were: Patients with NSTEMI-ACS who had multi-vessel CAD with $\geq 70\%$ diameter stenosis estimated visually or using quantitative coronary angiography

(QCA). Key exclusion criteria were: Patients with prior coronary bypass grafts, chronic total occlusions, acute ST segment elevation MI (STEMI), uncertain culprit lesions, left main disease, recent stroke, and patients with contraindications to dual antiplatelet therapy, associated co morbidities (liver failure, renal failure, and malignancy).

Methods

Baseline evaluation: All patients had review of medical history, demographic data (age, sex), risk factors for CAD (diabetes, hypertension, smoking, dyslipidemia), history of previous coronary interventions, heart failure, cardiac medications, comorbidities. Twelve leads Surface ECG immediately on admission and every 6 hours during first 24 hours, and once daily until discharge for assessment of ST-T wave changes and risk stratification of NSTE-ACS. Cardiac biomarkers: (Cardiac Troponin T or I & CK-MB at baseline and 6 hours later). Trans-Thoracic Echo Doppler: Transthoracic echocardiography was performed for all patients before coronary catheterization, and whenever indicated. We used the Hewlett Packard Sonos 5500®, equipped with phase array probe of 2.5-3.5 MHz. All patients were studied with M-mode, two dimensional echo to assess LV systolic function (ejection fraction) using Biplane Simpson method (Apical 4-chamber & apical 2-chamber) & to assess presence of RWMA for localization of coronary lesions if possible.

Coronary angiography and PCI: Patients received aspirin (300 mg loading then 150 mg daily), clopidogrel (300 mg loading then 150 mg /day maintenance dose for one week then 75 mg/day for one year). The technique proceeded through retrograde transfemoral arterial approach. A 6 Fr femoral arterial sheath was inserted; Un-fractionated heparin (UFH) (70 u/ kg) bolus dose was injected after sheath insertion. Coronary angiography was done. Standard coronary angiographic views were obtained to detect the culprit vessel, XB guiding catheters were used for left coronary lesions and JR catheters for RCA lesions. Glycoprotein inhibitors were used in lesions with heavy thrombus burden and or impaired TIMI flow after PCI. The operator determined the size and length of the stent, the sheath was removed 6 hours later from the end of PCI and compression was done manually. All patients received bare-metal or drug eluting stents either by direct stenting or pre-dilatation technique. The procedure was considered successful when the coronary stenotic lesions managed using stents without a residual stenosis (less than 10%), TIMI 3 flow and without procedure related complications.

Study protocol: Patients were subdivided into 2 groups according to PCI strategy:

- Group I: 25 patients who had been subjected to PCI of the culprit lesion only.
- Group II: 25 patients who had been subjected to PCI of all diseased vessels eligible for PCI (total revascularization).

Study end points: 30 days all cause mortality, myocardial infarction, need for emergency revascularization, recurrence of angina symptoms, and heart failure.

Statistical Analysis: The collected data was tabulated and analyzed using SPSS program (version 12.0). For presentation

of numerical (parametric data), mean and S.D. were used to describe both central tendency and dispersion of the data. In case of categorical (non parametric data), number and percentages were used for description. Independent sample t-test was used to compare numerical data between two different groups. Chi-square test for categorical data. P-value of less than 0.05 was used as an accepted level of significance to denote significant difference between groups.

Results

Study population

The mean age was 62 ± 12 years (62 ± 9 , 62 ± 13 in group I and II respectively, $p=0.85$). 70% were males (72% versus 68% in group I, II respectively, $p=0.75$). 32% with positive family history of CAD. 78% of patients had diabetes (79% versus 80% in group I, II respectively, $p=0.73$). 78% had hypertension (72% versus 84% in group I, II respectively $p=0.80$). 36% of patients had dyslipidemia (36% in both groups, $p=1.00$). 30% were smokers (32% versus 28% in group I, II respectively $p=0.75$). 24% of all patients had prior MI. PVD was reported in 10% of patients, while renal impairment was evident in 20% of patients. Comparison between groups showed no statistical significant difference in baseline clinical characteristics and risk factors between study groups (Table 1).

Clinical presentation on admission: Chest pain was the main symptom on admission in both groups (100%), 32% of patients presented with dyspnea (28% in group I versus 36% in group II, $P=0.5$), 16% of patients presented with palpitations (12 % in group I versus 20% in group II, $P=0.4$).

Clinical examination on admission: The mean heart rate was 99 ± 33 bpm (92 ± 29 versus 106 ± 35 bpm in group I, II respectively, $P=0.15$), the mean SBP was 149 ± 23 mmHg (139 ± 21 mmHg versus 160 ± 19 mmHg in group I, II respectively, $P=0.002$), the mean DBP was 89 ± 10 mmHg (84 ± 10 mmHg versus 93 ± 8 mmHg, in group I, II respectively, $P=0.007$).

ECG on admission: Thirty four percent of patients had ST segment depression (22% in group I versus 12% in group II). 30% had T wave inversion (20% in group I versus 10% in group II). 20% had normal ECG with no significant changes (8% in group I versus 12% in group II). 16% of patients had other changes including (old MI, poor R wave progression, RBBB)

Cardiac Biomarkers: The mean cardiac troponin I in all patients was 2.3 ± 1.1 $\mu\text{g/l}$ (1.9 ± 0.9 , 2.1 ± 1.2 in group I, II respectively, $p=0.18$). The mean CK-MB level was 112 ± 35 $\mu\text{g/dl}$ (79 ± 12 , 68 ± 9 , in group I, II respectively, $p=0.46$). Based on cardiac troponin, there was 26 patients (52%) had NSTEMI (60%, 44% in group I, II respectively, $p=0.26$). 24 patients (48%) had unstable angina (40%, 56% in group I, II respectively, $p=0.37$) (Figure 1).

Echocardiographic Data on admission: The mean LVEF % in all patients was 48.95 ± 10.7 (49.9 ± 10.1 versus 48 ± 11.3 in group I, II respectively, $p=0.54$). The mean Wall Motion Score Index (WMSI) in all patients was 1.53 ± 0.37 (1.57 ± 0.35 versus 1.5 ± 0.40 in group I, II respectively, $P=0.55$). RWMA was recorded in 20 versus 19 patients in group I, II respectively, $P=0.73$. Between groups analysis showed no statistically significant difference.

Time from onset of symptoms to admission: The mean time was 4.1±2.5 hours in all patients (4.6±2.37 hours in group I, versus 3.2±2.48 hours in group II, P = 0.14), 44 % of all patients presented less than 6 hours (36 % versus 52 % in group I, 2 respectively, P = 0.4), 58 % were admitted between 6-12 hours from onset of symptoms (64 % in group I versus 48% in group II respectively, P = 0.5).

Coronary angiography before PCI: Sixty percent of all patients had 2 - vessel disease, 40% of patients had 3 - vessel disease. Analysis between groups showed that 56% versus 64% in group I, II had 2 - vessel disease respectively (p=0.7), while 44% versus 36% in group I, II had 3- vessel disease respectively (p =0.7).

LAD was affected in 90% of patients (88% versus 92% in group I, II, respectively p= 0.7), while RCA in 60% of all patients (68% versus 52% in group I, II respectively, p= 0.7). LCX in 64% of all patients (68% versus 60% in group I, II respectively, p=0.7). Culprit artery was LAD in 60% of all patients (64% versus 56 % in group I, II respectively, P = 0.37), RCA was the culprit artery in 16% of patients (20% versus 12% in group I, II respectively, P =0.37), while LCX was the culprit artery in 24 % of patients (16% versus 32% in group I, II respectively, p=0.37). TIMI flow pre PCI was TIMI flow II in 44% of all patients (40% versus 48% in group I, II respectively P =0.4), while TIMI flow III was present in 56% of all patients (60% versus 52% in group I, II respectively P =0.4) (Table 2).

Table 1: Baseline characteristics of study population.

	All Patients No =50	Group I Culprit Revascularization group	Group II Total Revascularization group	P Value
Age, years Mean ± SD	62±12	62± 9	62 ± 13	0.85
Male Sex, n (%)	35 (70%)	18 (72%)	17(68%)	0.75
Family history of CAD	16 (32%)	7 (28%)	9 (36%)	0.54
DM	39 (78%)	19(76%)	20 (80%)	0.73
Hypertension	39 (78%)	18 (72%)	21(84%)	0.8
Smoking	15 (30%)	8 (32%)	7 (28%)	0.75
Dyslipidemia	18 (36%)	9 (36%)	9 (36%)	1
Prior MI	12 (24%)	6 (24%)	6 (24%)	1
Prior PVD	5 (10%)	3 (12%)	2 (8%)	0.36
Prior renal Dysfunction	10 (20%)	5 (20%)	5 (20%)	1

DM: Diabetes Mellitus; MI: Myocardial Infarction; PVD: Peripheral Vascular Disease

Table 2: Baseline angiographic data.

	All patients	Group I	Group II	P value
	No = 50	No = 25	No = 25	
TIMI flow pre PCI II	22 (44%)	10 (40%)	12 (48%)	
III	28 (56%)	15 (60%)	13 (52%)	0.49
Culprit artery				
LAD	30 (60%)	16 (64%)	14 (56%)	
RCA	8 (16%)	5 (20%)	3 (12%)	0.37
LCX	12 (24%)	4 (16%)	8 (32%)	
Number & type of artery				
LAD	45 (90%)	22 (88%)	23 (92%)	
RCA	30 (60%)	17 (68%)	13 (52%)	
LCX	32 (64%)	17 (68%)	15 (60%)	
3- vessel disease	20 (40%)	11 (44%)	9 (36%)	0.71
2- vessel disease	30 (60%)	14 (56%)	16 (64%)	

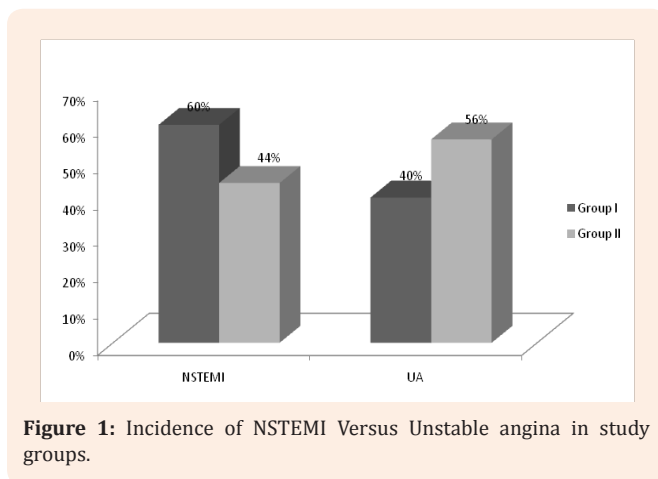


Figure 1: Incidence of NSTEMI Versus Unstable Angina in study groups.

PCI data: All patients received 10000 units of UFH pre PCI, femoral approach was done in all patients using 6 fr sheath, XB guiding catheter was used in 50% of patients while JR was used in 10% of patients, while in 40% of patients XB and JR were used, floppy wire was used in 90% of patients, while coated wire in 10 % of patients, predilatation was done in 56% of patients, glycoprotein inhibitors were used in 20% of patients (16% versus 24% in group I, II respectively, $P=0.32$). The stent number was one in 40% of all patients (80% versus 0% in group I, II respectively, $P=0.001$), while two stents in 34% of patients (20% versus 48% in group I, II respectively, $P=0.001$), three stents were inserted in 22 % of patients (0 % versus 44% in group I, II respectively, $P=0.001$), while four stents were inserted in 4% of patients (0% versus 8% in group I, II respectively, $P=0.001$), the mean stent length was 21.8 ± 5.63 mm (23.95 ± 5.11 mm versus 20.72 ± 5.62 mm in group I and group II respectively, $P = 0.03$), the mean stent diameter was 2.87 ± 0.28 mm (3.0 ± 0.3 mm versus 2.8 ± 0.28 mm in group I, II respectively, $P=0.01$), BMS used in 88% of patients (84% versus 92% in group I, II respectively, $p=0.6$) while BMS-DES used in 12% of patients (16% versus 8% in group I, II respectively, $p=0.6$). TIMI flow in culprit artery after PCI was III in 98% of patients (96% versus 100% in group I, II respectively, $p=0.1$), while TIMI flow II was present in 2% of patients (4% versus 0% in group I, II respectively, $p=0.1$), the mean procedural time was 48.42 ± 13.49 minutes in all patients (40.30 ± 8.59 min versus 56.55 ± 14.74 min. in group I, II respectively, $P = 0.003$). The mean contrast volume was 227.95 ± 78.6 ml in all patients (169.5 ± 74.5 ml versus 286.4 ± 58.1 ml in group I, II respectively, $P = 0.001$). Acute vessel occlusion occurred in one patient versus 2 patients in group I, II respectively, caused by either occlusion of a side branch, De novo thrombosis or acute stent thrombosis, which was managed successfully by PTCA plus intracoronary glycoprotein inhibitors and nitroglycerin injection. Dissection occurred in one patient in group I which was managed successfully with stenting. Arrhythmia, ventricular tachycardia occurred in one patient in Group II due to acute vessel occlusion and was managed with cardioversion. No reported cases of perforation, major bleeding, no reflow or mortality.

In hospital outcome: No reported cases of cardiogenic shock, major bleeding or mortality in either group. Recurrence of chest

pain was reported in 20% of patients (20% in both of group I, II, $P=1.0$), post procedural infarction was reported in 6% of patients (4% versus 8% in group I, II respectively, $p=0.55$). Contrast induced nephropathy was evident in 24% of patients (20% versus 28% in group I, II respectively, $p=0.3$), minor bleeding occurred in 17% of patients (10% versus 25% in group I, II respectively, $P =0.4$), stent thrombosis occurred in 5% of patients (10% of group II and non in group I, $P=0.4$), heart failure occurred equally in both groups (10%), also arrhythmia was reported equally in both groups (15%).

Thirty-days outcome: There was no recorded cases of mortality in both groups at 30 days. Re-hospitalization was reported in 8 (16%) patients, 5 (20%) versus 3 (12%) in group I, II respectively, $p=0.15$. Target or new target revascularization was reported in 3 (6%) patients, all of them (12%) were in group I but none were reported in group II, $p=0.03$, Three from 5 re-hospitalized patients underwent PCI or PTCA in group I versus non from the 3 re-hospitalized patients underwent PCI or PTCA in group II. Re-infarction was reported in 2 patients (4%) of all patients, (all the 2 patients were in group I (8%) but none in group II, $p=0.14$). The 2 re-infarcted patients had been re-hospitalized then coronary angiography was done, in one case 1ry PCI to proximal RCA lesion while PTCA to LAD in-stent restenosis was done. Primary PCI to RCA was complicated with no reflow which was managed pharmacologically (using intracoronary tirofiban, verapamil and nitroglycerin) and then maintained on tirofiban infusion for 24 hours.

Follow up Echocardiography: The mean baseline EF % in all patients was 48.8 ± 10.7 (49.5 ± 10.1 versus 48.11 ± 11.3 in group I, II respectively, $p=0.5$). At 30 days, the mean EF% in all patients was 50.9 ± 11 ($50.3\% \pm 10.7$ versus $51.6\% \pm 11.6$ in group I, II respectively, $p=0.6$).

Discussion

Patients with NSTE-ACS frequently demonstrate multivessel coronary artery disease [7]. For those deemed at moderate or high risk, an early invasive strategy is recommended, and results in improved clinical outcomes. Although electrocardiographic and angiographic signs may help identify the culprit lesion(s) responsible for the acute presentation among patients with NSTE-ACS, it is well documented that multiple segments of the coronary tree exhibit plaque disruption or frank rupture, presumably related to a heightened inflammatory milieu [8]. The patients deemed candidates for PCI during NSTE ACS more typically undergo treatment of the culprit lesion alone rather than MV revascularization. Single vessel PCI is perceived to have a more favorable benefit-to-risk ratio and financial implications while avoiding the potential complications arising from increased contrast material and radiation administration as well as the rare but existent danger of having >1 jeopardized territory at the same time associated with MV PCI. Yet, the data supporting these issues are relatively sparse [9]. In this study, we examined the safety and efficacy of multivessel PCI compared with culprit-only PCI in patients with MVD presenting with NSTE-ACS. We did not report statistically significant differences in peri-procedural complications between both groups. However, PCI time, contrast volume, was significantly higher in total revascularization group.

Thirty days clinical outcome was similar in both groups but there was significantly higher rate of need for re-intervention in culprit lesion PCI patients. In the present study we reported 2 vessel disease and 3 vessel disease in 60%, and 40% of the study population respectively, 3-vessel disease was 44% vs 36% in group I, II respectively. In the study by Hasin et al. [10], 3-vessel disease represented 43% vs 41% in SVR, MVR respectively. However, Marino et al. [11] showed that 3-vessel disease was evident in 40% vs 42% in single vessel PCI, multivessel PCI respectively. This variation in the number of vessels affected may be explained by the difference in the profile of risk factors between different studies. We reported LAD lesion in 88% vs 92% in group I, II respectively. In the study by Hyun Jong Lee et al. [10] proximal LAD lesion was reported in 53% vs 57% in SVR, MVR groups respectively. However, in the study derived by Shishehbor et al. [2] LAD lesion was reported in 36% vs 45% in culprit-only stenting and multivessel stenting respectively. The mean PCI time was significantly longer in patients assigned to total revascularization versus in those who had culprit only PCI. In addition there was larger volume of contrast material in total revascularization patients compared to culprit only PCI patients [12] reported that in MVR group the mean fluoroscopic exposure time was 16 minutes, while in the SVR group the mean fluoroscopic exposure time was 11 minutes. This was logic, because some extra time and contrast was needed to treat the non culprit artery lesions. Thirty days outcome showed higher incidence of re-hospitalization in group I (20%) than in group II (12%) but of no significant difference ($p=0.15$). Target or new target revascularization was reported in group I only (12%), no reported cases in group II. No recorded cases of mortality through one month follow up.

In agreement with the present study, Ijsselmuiden et al. [13] investigated the major cardiac events at short and long term follow-up of multi-vessel versus culprit-vessel stenting in patients presenting with NSTEMI-ACS and multi-vessel disease (MVD). MACE rates at 1 month (14.4% vs 9.3%), 1 year (32.4% vs 26.9%), and 4.6 +/- 1.2 years (40.4% vs 34.6%) were similar in both groups. Repeat PCI was performed more often in the culprit vessel group (31.2% vs 21.2%, $P=0.06$). Shishehbor et al. [2] compared the safety and efficacy of non-culprit multi-vessel compared with culprit-only stenting in patients with multi-vessel disease presenting with NSTEMI-ACS in 1,240 patients with ACS and multi-vessel CAD underwent PCI with bare-metal stenting and met their study criteria. Of these, 479 underwent multi-vessel and 761 underwent culprit-only stenting. There were 442 events during a median follow-up of 2-3 years. They concluded that multi-vessel intervention was associated with lower death, myocardial infarction, or revascularization after both adjusting for baseline and angiographic characteristics. Brener et al. [12] reported that multi-vessel PCI appeared to be associated with at least as successful an in hospital outcome as single vessel PCI. Procedural success was achieved in 91% of single vessel PCI and 88% of multi-vessel PCI ($P<0.001$). They reported an in-hospital mortality was 1.3% and 1.2%, respectively ($P=0.13$). Rates of morbidity, such as bleeding, development of renal failure, or non fatal cardiogenic shock, were similar for both groups. These results were agreed with the present study. In agreement with our study, Zapata et al. [14] investigated the major cardiac events at 1-year follow-up of multi-vessel versus culprit-vessel stenting in patients presenting with NSTEMI-ACS and multi-vessel disease (MVD). The incidence

of MACE was lower in MVR (9.45% vs. 16.34%, $P=0.02$) with lower revascularization rate (7.46% vs. 13.86%, $P=0.04$) than in CVR. There was no difference in death (1.99% vs. 1.98%, $P=0.8$) nor death/MI (2.49% vs. 3.22%, $P=0.8$) between MVR and CVR, respectively. Multivariate analysis showed CVR as the only independent predictor of improved MACE ($P=0.01$). Multi-vessel stenting in patients with NSTEMI-ACS and multi-vessel disease using a clinical decision of treatment is associated with lower rate of MACE driven by lower repeat revascularization, compared with culprit-vessel stenting, without significant difference in rates of death or MI.

Multivessel revascularization may afford advantages in greater myocardial salvage or reducing myocardial ischemia, whereas it can result in greater myocardial damage or higher exposure to radiocontrast agent compared with SVR.

Conclusion and Recommendations

Percutaneous multivessel CAD intervention is feasible, efficient and safe compared with culprit vessel stenting in patients with MVD presenting with NSTEMI-ACS. The decision of whether to perform culprit vessel or complete revascularization can be made on an individual basis. Further larger randomized long term studies are recommended to confirm the benefit of multivessel revascularization in this clinical setting.

Limitations of the Study

- Small sample size.
- The severity and location of the coronary lesions are based on operator visual estimation.
- The decision to perform MVR or SVR in each patient was at the operator's discretion.
- No exact comparison between DES & BMS.
- Short follow up period.
- Non randomized design.

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