The Egyptian Journal of Hospital Medicine (April 2024) Vol. 95, Page 1714- 1721

Fractional Flow Reserve–Guided Percutaneous Coronary Intervention (PCI) as Compared with Coronary Bypass Surgery in Patients with Three-Vessel Coronary Artery Disease

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ABSTRACT

Background: It has been demonstrated that patients with three-vessel coronary artery disease respond better to coronary-artery bypass grafting (CABG) than to percutaneous coronary intervention (PCI).

Aim of the Study: To compare the incidence of significant adverse cardiac or cerebrovascular events in patients with three-vessel coronary artery disease between fractional flow reserve (FFR) -guided PCI using current-generation drug-eluting stents and CABG.

Patients and methods: One hundred patients with three-vessel coronary artery disease, identified angiographically and not involving the left main coronary artery, were included in this randomized prospective clinical study. This study comprised 100 patients who were randomly assigned into two groups: **Group I:** 50 patients underwent FFR-guided PCI. **Group II**: 50 patients underwent CABG.

Results: The CABG group received an average of 3.7 distal anastomoses, with 34% receiving multiple arterial grafts and 92% receiving a left internal thoracic artery graft. The primary endpoint of MACCE was lower in the FFR-guided PCI group (6%) compared to the CABG group (10%). Secondary endpoints like death, spontaneous MI, stroke, and revascularization were generally higher in the CABG group, while target vessel revascularization was higher in the PCI group. Regarding safety, the PCI group had a significantly lower incidence of BARC type 3-5 bleeding (2% vs 16%) and atrial fibrillation (10% vs 28%) compared to CABG. Acute kidney injury and 30-day rehospitalization rates were insignificantly different between the groups.

Conclusion: The FFR-guided PCI group had a lower incidence of MACCE at 6% compared to 10% in the CABG group.

Keywords: Fractional Flow Reserve–Guided Percutaneous Coronary Intervention, Coronary Bypass Surgery, Three-Vessel Coronary.

INTRODUCTION

Heart disease is the leading cause of death globally, or CAD. It has been demonstrated that revascularization of coronary arteries that are producing ischemia improves outcomes as compared to medical therapy, particularly in cases when a sizable ischemic area is at risk [(1)].

The first method of revascularization that was widely available was in individuals with severe coronary disease. Coronary artery bypass graft (CABG) has been demonstrated in multiple trials to be more effective than pharmaceutical therapy over 50 years ago [(2)].

One of the main points of contention regarding the best course of treatment for a patient with 3-vessel CAD (3-VD) has been the type of revascularization, ever since PCI was introduced in 1977 as an alternative to CABG surgery [(3)].

Extensive randomized trials have demonstrated that coronary artery bypass grafting (CABG) is a better method of coronary revascularization for individuals with three-vessel coronary artery disease than is percutaneous coronary intervention (PCI). However, drug-eluting stents of the second generation have not been often employed in studies, and fractional flow reserve (FFR) has not been regularly assessed to direct PCI [(4)].

Fractional flow reserve (FFR), gauges stenotic artery's maximum blood flow as a proportion of the maximal flow normal and is used to evaluate the importance of coronary stenosis physiologically. This ratio is simple to determine during the procedure: the greatest hyperemia during coronary angiography divided by the aortic pressure obtained concurrently with the guiding catheter to determine the distal coronary pressure utilizing a coronary pressure guidewire. 90% accuracy is achieved in distinguishing coronary stenoses that cause ischemia when the FFR value is 0.80 [(5)].

Prior research has indicated that improved outcomes are associated with FFR guided PCI. The fractional flow reserve vs angiography for multivessel evaluation (FAME) study's findings demonstrated that FFR guided therapies yielded superior outcomes. Subsequently, the second research, dubbed FAME II, compared medical care with FFR-guided PCI. This trial was abruptly stopped because a far greater proportion of patients who were receiving only medical care needed immediate revascularization [(6)].

This study aimed to assess the frequency of major adverse cardiac or cerebrovascular events in patients with coronary artery disease in three vessels over the

Received:15/11/2023
Accepted:15/01/2024

period between CABG and FFR-guided PCI with current-generation drug-eluting stents.

PATIENT AND METHODS

One hundred patients with three-vessel coronary artery disease, identified angiographically and did not involve the coronary artery that is left major, were included in this randomized prospective clinical study.

Inclusion criteria:

- Both sexes
- Age >18 years old
- The presence of three-vessel coronary artery disease.

Exclusion criteria

- Age<18 years old.
- The need for additional cardiac or non-cardiac surgical procedures (such carotid revascularization or valve replacement).
- Hemodynamic support being necessary or cardiogenic shock using medication or a machine.
- New STEMI (less than five days before randomization).
- Persistent non-STEMI with persistently growing cardiac troponin levels.
- A documented LV ejection fraction of less than 30%.
- Expectation of life < 2 years.
- Needing treatment for renal replacement.
- Getting assessed in order to receive an organ transplant.
- Taking part in or intending to take part in another clinical experiment, with the exception of observational registries.
- Being pregnant.
- Not being able to take two antiplatelet medications for a whole six months.
- The earlier CABG.
- Disease of the left main that needs revascularization.
- Vascular structures that are too hardened or twisted to allow for FFR measurement.
- Every target lesion that has drug-eluting stent restenosis within it.

Randomization and blindness

Two groups of patients were allocated at random (using a random sequence produced by a computer with a 1:1 ratio).

Group I: FFR-Guided PCI: 50 patients stent all lesions with FFR ≤0.80.

Group II: CABG 50 patients based on coronary angiogram.

All studied cases were subjected to the following:

A. Detailed history taking, including:

- Individual history, including name, age, gender, and BMI (body mass index).
- Current history: length and course of the illness.
- **Risk factors including h**ypertension, diabetes mellitus, hyperlipidemia, cardiovascular disease, cardiac arrhythmia, myocardial infarction in the past (MI), prolonged obstruction of the airways (COPD), chronic kidney disease (CKD), family history and cigarette smoking

B. Patient clinical presentation including:

- Chest pain, dyspnea

C. Full clinical examination

- Vital indicators such as blood pressure, heart rate, and saturation of oxygen and temperature.
- Laboratory investigations including CBC, lipid profile, K, Na, creatinine, blood urea nitrogen, troponin I, CKMB and CRP.

D. Mechanical complications, and signs of heart failure by Killip classification (.

Table ().

Table (1): Killip classification of acute myocardial infarction* [7-9]

Class	PAO2†	Clinical description
1	Normal	No clinical evidence of left ventricular (LV) failure
2	Slightly reduced	Mild to moderate LV failure
3	Abnormal	Severe LV failure, pulmonary edema
4	Severely abnormal	Cardiogenic shock: hypotension, tachycardia, mental obtundation, cool extremities, oliguria, hypoxia
* Determined by repeated examination of the patient during the course of illness.		
† Determined while the patient is breathing room air.		

Baseline electrocardiography:

The accepted method for assessing the electrical function of the heart is an ECG. A 12-lead ECG's conventional electrode placement placed the leads on the left and right arms as well as both the left and right legs. On the sternum's left and right sides, another set of electrodes were positioned in the space between the fourth and fifth ribs. In the fourth intercostal gap, one electrode was placed in between these two electrodes.

Echocardiography:

Echocardiography was performed to all patients. 67 ± 8 frames/sec were the mean frame rates of digital routine grayscale two-dimensional cine loops, which measure 12-14 cm, were recorded using three consecutive heartbeats of the usual three apical views at depths and the parasternal long-axis view of end-expiratory apnea.

Ethical considerations:

The Ethics Committee of the Faculty of Medicine, Department of Cardiology, Benha University Hospital gave its approval to the project. An informed written consent was obtained from all patients. Each subject was given a secret code number as well as an explanation of the study's objective.

Statistical Analysis

The statistical analysis was performed using SPSS v28 from IBM©, Chicago, IL, USA. Quantitative data were presented as mean, standard deviation (SD), range, median, and interquartile range (IQR) and were compared by independent t-test or Mann-Whitney test. Qualitative data were presented as frequency and percentage and were compared by Chi-Square test or Fisher's exact test. P value < 0.05 was considered significant.

RESULTS

Table (shows that there were insignificant differences between the studied groups regarding the LVEF and SYNTAX score.

Table (2): LVEF and SYNTAX score of the studied groups

		Group I (n=50)	Group II (n=50)	P value
LVEF %	**Mean ± SD**	51.9 ± 7.75	52.5 ± 6.77	0.691
	Range	40 - 65	40 - 64	
SYNTAX score	**Mean ± SD**	27.9 ± 4.89	28.3 ± 3.59	0.642
	Range	20 - 34	22 - 34	

LVEF: left ventricular ejection fraction.

Regarding the procedural characteristics, time to procedure was significantly higher in group I compared to group II, while procedure duration was significantly lower in group I compared to group II. ICU stay and hospital stay were significantly lower in group I compared to group II **[Table (]**.

Table (3): Procedural characteristics of the studied groups

		Group I (n=50)	Group II (n=50)	P value
Time to procedure (days)	**Mean ± SD**	16.8 ± 6.44	8.3 ± 3.29	**<0.001***
	Range	7 - 28	3 - 13	

	Median (IQR)	15 (11.2-22)	8.5 (6-11)	
Procedure duration (min)	**Mean ± SD**	91.6 ± 11.87	197.1 ± 19.7	**<0.001***
	Range	72 - 113	157 - 229	
	Median (IQR)	92 (82-101.5)	198(185.2- 211.2)	
ICU stay (days)	**Mean ± SD**	2.9 ± 0.82	8.8 ± 2.73	**<0.001***
	Range	2 - 4	3 - 13	
	Median (IQR)	3 (2 - 4**)**	9.5 (7 -11)	
Hospital stay (days)	**Mean ± SD**	4.3 ± 1.62	11.7 ± 2.78	**<0.001***
	Range	2 - 7	8 - 17	
	Median (IQR)	4 (3 - 5.75)	12 (9 - 14)	

In the FFR-guided PCI group, the mean number of stents was of 3.6 ± 0.83. The mean total length of stents placed was 83.8 ± 18.5 mm **[**Error! Not a valid bookmark self-reference.**].**

Table (4): FFR-guided PCI characteristics of the studied groups

		Group I (n=50)
Staged procedure		15 (30%)
No. of stents	**Mean ± SD**	3.6 ± 0.83
	Range	2.3 - 4.9
Total length of stents placed (mm)	**Mean ± SD**	83.8 ± 18.5
	Range	53 - 115
Intravascular imaging used		10 (20%)

Patients undergoing CABG received distal anastomoses with a mean of 3.7 ± 0.74. 92% patients received a left internal thoracic artery graft **[**Error! Reference source not found.**].**

Table (5): CABG characteristics of the studied groups

		Group II (n=50)
No. of distal anastomoses	**Mean ± SD**	3.7 ± 0.74
	Range	2.4 - 4.9
Multiple arterial grafts		17 (34%)
LITA used as graft		46 (92%)
Off-pump surgery		8 (16%)
FFR used before CABG		7 (14%)

Group I had a significantly reduced incidence of BARC type 3–5 hemorrhage and atrial fibrillation than Group II. Other endpoints at 1-year were insignificantly different between both groups **[**Error! Not a valid bookmark self-reference.**]**.

Table (6): End points at 1-year of the studied groups

	Group I (n=50)	**Group II (n=50)**	**P value**
Primary endpoints			
MACCE	3 (6%)	5 (10%)	0.715
Secondary endpoints			
Death	2 (4%)	5 (10%)	0.715
Spontaneous MI	2 (4%)	6 (12%)	0.269
Stroke	2 (4%)	7 (14%)	0.159
Revascularization	2 (4%)	4 (8%)	0.678
Target vessel revascularization	5 (10%)	3 (6%)	0.715
Safety endpoints			

BARC type 3–5 bleeding	1 (2%)	8 (16%)	**0.031***
Acute kidney injury	1 (2%)	6 (12%)	0.112
Atrial fibrillation	5 (10%)	14 (28%)	**0.022***
Rehospitalization within 30 days	1 (2%)	6 (12%)	0.112

MACCE: Major adverse cardiac and cerebrovascular events, MI: Myocardial infarction, BARC: Bleeding Academic Research Consortium.

DISCUSSION

We found the LVEF and SYNTAX scores did not vary appreciably among the study groups. **Fearon *et al.*** demonstrated that there was no discernible difference in the ejection fraction between the two groups ≤50% [(4)]. Additionally, **Zimmermann *et al.*** reported that LVEF and SYNTAX scores between the two groups did not differ substantially [(10)].

Regarding the comparison between the FAME-3 trial, which aims to guide PCI and coronary bypass surgery using fractional flow reserve, **Bonaros** found the mean SYNTAX scores of patients with PCI and CABG did not differ statistically significantly, which were 26.0 and 25.8, respectively [(11)].

Regarding the procedural characteristics, group I underwent a longer longer time to procedures (P<0.001) than group II, while group I underwent a significantly shorter time to procedures (P<0.001). Group I had a considerably shorter ICU stay and hospital stay than Group II (P<0.001).

In agreement with our study, **Fearon *et al.*** discovered that the median time to procedure differed significantly (P<0.001) between the two groups. In contrast to the CABG group, the PCI group experienced a considerably shorter median hospital stay and ICU stay [(4)].

Also**, Zimmermann *et al.*** reported that the mean procedure duration was 87 (67–113) minutes in the PCI group and 197 (155–239) minutes within the CABG cohort. The PCI procedure took 13 days to complete and the procure took 4 days for the CABG group. The PCI group's length of stay was 3 (1–7), while that of CABG group was 11 (7–16). Compared to the PCI group, the CABG group's mean procedure duration was much greater. Compared to the CABG group, the PCI group's hospital stay was substantially shorter [(10)].

Head *et al.* performed a prospective investigation that split patients into two groups: Thirty patients underwent CABG in Group A, while fifty patients underwent PCI in Group B. Regarding the overall number of procedures (grafts or stents), the two groups did not differ in any noticeable way. But the surgical method required more time for the operational, bypass, and ischemic phases, and the CABG group required pharmacological support throughout the weaning process from the bypass. In the CABG group, a lengthier ICU was also discovered [(12)].

We observed that in the FFR-guided PCI group, 15 (30%) patients underwent a phased process. The range of stent counts was 2.3 - 4.9 with a mean of 3.6 ± 0.83. The overall length of the inserted stents varied from 53 - 115 mm with a mean of 83.8 ± 18.5 mm. In ten patients (20%), intravascular imaging was used. Distal anastomoses ranged from 2.4 to 4.9 with a mean of 3.7 ± 0.74 were given to CABG patients. Multiple arterial grafts were given to 17 (34%) patients, and left internal thoracic artery grafts were given to 46 (92%) patients. Eight (16%) patients had off-pump surgery, and seven (14%) patients had FFR evaluated prior to CABG.

Fearon *et al.* revealed that the average number of lesions, minutes each patient had in the FFR-guided PCI group, was 4.3. The median stented length was 80 mm, and the average 82% of patients had 3.7 drug-eluting stents. Vessels that were partially or wholly obstructed, were the most frequent causes of failure to measure FFR. Twenty-four percent of the lesions that were going to be treated had an FFR higher than 0.80, with a mean FFR of 0.70. FFR was assessed with a mean value of 0.88 following PCI in 60% of treated lesions. In 12% of cases, intravascular imaging was employed. 97% of CABG patients underwent many arterial grafts, including a left internal thoracic artery graft. Patients had an average of 4.2 lesions and 3.4 distal anastomoses. FFR was assessed in 10% of patients prior to CABG [(4)].

In the FREEDOM experiment, the overall stent length was substantially shorter than in this trial, even

with more severe coronary disease[4]. **Zimmermann *et al*.** found that mean no. of stents was 3.7±1.9 and mean total length of stents placed was 80 (52–116) mm in PCI. No. of distal anastomoses was 3.4±1.0 in CABG group [10].

In our study, three patients (6%) in groups I and 5 experienced MACCE related to the primary objectives (10%) patients in group II. Two percent of patients in group I and five percent of patients in group II died; two percent of patients in group I and six percent of patients in group II experienced spontaneous MI; two percent of patients in group I and seven percent of patients in group II experienced strokes; two percent of patients in group I and four percent of patients in group II underwent revascularization; and five percent of patients in group I and patients 3 in group II underwent target vessel revascularization.

According to a prior study, the major end point was determined by combining the variables for death, MI, CVA, and MACCEs. The main factor influencing the difference (13.5% vs 5.9%, P <0.001) was a considerable increase in the requirement for repeat revascularization, despite a significant trend toward lower incidence of MI (4.8% vs 3.3%, P =0.11) and cardiac death (3.7% vs 2.1%, P =0.05) in the CABG arm. These occurrences were mostly offset by a much-reduced rate of CVA in the PCI arm (0.6% vs 2.2%, P =0.003). The 5-year follow-up of this trial showed that the PCI arm had a significantly higher risk of MI (9.7% vs 3.8%, P = 0.0001) and cardiac mortality (9.0% vs 5.3%, P =0.003), in addition to a notably higher rate of MACCE (37.3% vs 26.9%, P <0.0001) [10].

The results of SYNTAX are validated by the FREEDOM trial. At the 5-year follow-up, the primary end result (death, MI, or CVA) was considerably more common in the PCI arm of this research, which randomly assigned 1,900 diabetic individuals to either PCI or CABG (26.6% vs. 18.7%, P =0.005). The main causes of this discrepancy were higher MI and greater CVA rates in the CABG arm and death rates in the PCI arm [13].

During the SYNTAX trial, 1,800 individuals with severe left main coronary disease or 3-VD were randomly assigned to receive PCI or CABG. The results showed that the PCI group had considerably greater primary end point rates after a year, P =0.002, 17.8% vs. 12.4% [14].

These days, the majority of 3-VD patients receive CABG recommendations on a regular basis, particularly if their SYNTAX score is high or intermediate. However, with PCI FFR guidance and maybe most crucially, contemporary stent technology could improve the poor results of PCI as evidenced by SYNTAX and FREEDOM[10].

Fractional flow reserve is a metric that determines the ischemia potential of a coronary stenosis using coronary pressure wires. The average proximal heart rate can be calculated by dividing it by the mean distal coronary pressure, it is computed during a state of maximal hyperemia. Several studies have shown that revascularization is necessary if the FFR is less than 0.80, which indicates the presence of severe ischemia associated with that stenosis. On the other hand, even though the lesion appears angiographic, it can be safely treated with medication if the FFR is N0.80, and a good result is anticipated [15].

The possible advantages of FFR, first, the use of FFR in routine practice settings in many hospitals is frequently left up to the operator's judgment based on angiographic data. Furthermore, there is a well-known lack of correlation between a coronary stenosis's angiographic appearance and functional relevance. Therefore, in cases where FFR is not routinely employed, certain functionally severe lesions that appear to cause mild to moderate artery narrowing based on visual inspection may not have been considered for PCI. Alternatively, certain hemodynamically inconsequential lesions may be visually regarded as serious, leading to needless PCI even if they may have a better prognosis [16].

Furthermore, FFR readings in the "grey zone" of 0.75 to 0.80 were formerly thought to necessitate clinical discretion when making decisions about revascularization. But still, **Legalery *et al.*** showed that it was detrimental to postpone PCI in lesions with FFR < 0.80 [17].

To reduce the number of ischemic lesions that remain untreated, more recent research used the top limit of this narrow transition zone as a PCI threshold [18,19].

Data of **Sant'Anna *et al.*** showed that the FFR-Defer group performed better than the FFR-Perform group, which strongly suggests using FFR to determine if PCI may be safely postponed. Furthermore, the FFR-guided group had a considerably reduced number of stents inserted even though some patients had PCI in an artery with FFR >0.80 [20].

Similar to this, a recent analysis of the FAME research demonstrated that by lowering stent use, rehospitalizations, and MACE, FFR-guided PCI led to a significant cost savings. Therefore, if PCI decision-making depends more heavily on FFR value, the therapy guided by FFR may have been more cost-effective in everyday practice [21].

By the way, the usage of FFR between 2003 and 2009 indicated a brief decrease in the middle of the years, which was abruptly followed by an increase in 2009. This might be an indication of how clinical practice has changed since the historic FAME study was published in January 2009[22].

A total of 1,005 people with stable symptoms, acute coronary syndromes without ST elevation, or two or three-vessel coronary disease were randomized in the FAME trial to receive either FFR-guided PCI or

angiography-guided PCI, where PCI was carried out only if the FFR was ≤0.80.24[22].

Although there was a tendency toward a fall in the incidence of MI, mortality, and FFR-guided PCI was still linked to a statistically significant decrease in death at the 2-year follow-up and MI (8.4% vs 12.9%, P =0.02), despite repeated revascularization (17.9% vs. 22.4%, P = 0.08) [15].

A previous study found that at one year, the incidence of the primary end point was 6.9% in the CABG group and 10.6% in the FFR-guided PCI group (hazard ratio: 1.5; 95% confidence interval: 1.1 to 2.2; P=0.35 for noninferiority). It did not seem to be a significant difference between the groups in the frequency of any one component of the primary end point or the composite death rate, myocardial infarction, or stroke. The medical therapy used in the groups did not change significantly after a year, albeit a higher percentage of patients receiving dual antiplatelet and nitrate medication were part of the FFR-guided PCI group. Patients who were randomly allocated to receive CABG had longer hospital stays, higher rates of significant bleeding, arrhythmia, acute renal impairment, and 30-day hospital readmissions [4].

Fearon *et al.* discovered that after a year, FFR-guided PCI and CABG (which made use of the newest type of zotarolimus-eluting stents) reduced composite incidence of stroke, recurrent revascularization, myocardial infarction, and mortality. There was no statistically significant difference in the incidence of any individual component of the primary end point or the secondary composite end point of mortality, myocardial infarction, or stroke between the two groups [4].

Acute renal impairment, arrhythmia, significant bleeding, and 30-day readmission were the most frequent procedure-related complications encountered by individuals who were randomized to get CABG. They also had longer average hospital stays [4].

Patients assigned to PCI in a previous trial reported lower death rates (1.6% vs. 4.4%) and a decreased risk of recurrent revascularization (4.9% vs. 13.5%) compared to the SYNTAX study, despite the fact that there are no direct comparisons between these experiments. However, patient demographics and risk profiles were similar between the two studies. These findings may be explained by fewer stent implantations (which reduces the danger of thrombosis or restenosis), better stent technology, and a high proportion of patients who adhere to their doctors' instructions. Furthermore, compared to patients randomly slated to receive CABG treatment in the SYNTAX study (12.4%), individuals scheduled for FFR-guided PCI (10.6%) or CABG (6.9%) in their trial had a decreased prevalence of significant adverse cardiac or cerebrovascular events[14].

Better surgical methods or more potent medication therapy may have contributed to the trial's better results among the CABG participants. For instance, in this trial, the proportion of patients allocated to have CABG who were taking beta-blockers or statins after one year was 83% and 94%, respectively, contrasted with between 70% and 75% in the SYNTAX study, respectively[23].

Regarding the safety endpoints, 1 (2%) patient in group I and 8 (16%) patients in group II experienced BARC type 3–5 bleeding; 1 (2%) patient in group I and 6 (12%) patients in group II experienced acute kidney injury; 5 (10%) patients in group I and 14 (28%) patients in group II experienced atrial fibrillation; and 1 (2%) patient in group I and 6 (12%) patients in group II experienced rehospitalization within 30 days. Group I had a significantly reduced incidence of atrial fibrillation and hemorrhage; Academic Research Consortium category 3–5 hemorrhage, than group II (P=0.031 and 0.022, respectively). Acute renal damage and readmission within 30 days, the final two one-year goals, showed very little difference between the two groups. According to a prior study, the PCI group experienced notably fewer BARC type 3–5 bleeding events, atrial fibrillation, acute renal impairment, and 30-day readmissions than the CABG group[4].

After undergoing both treatment regimens, diabetic individuals reported comparable rates of all-cause mortality, MI, or stroke after five years. However, compared to FFR-guided PCI, the rate of recurrent revascularization following CABG was reduced. Studies have shown that diabetic patients with MVD treated with CABG have reduced rates of hard end points when compared to PCI. However, in these investigations, the choice to revascularize was mostly made based on an assessment of the angiographic severity that was visible. Assessing the angiographic severity in patients with diabetes can be much more difficult than in those without the disease [12,24].

CONCLUSION

Regarding the procedural characteristics, procedure duration, ICU stay, hospital stay, BARC type 3–5 bleeding, the PCI group experienced much less complications than the CABG group. In terms of the incidence of a composite of death (MACCE), which happened in 3 patients (6%) in the FFR-guided PCI group and 5 patients (10%) in the CABG group among patients with three-vessel coronary artery disease, FFR-guided PCI was considered noninferior to CABG. At one year, revascularization, death, MI that occurred on its own, and stroke were the secondary outcomes.

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