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Original Research Article

FRACTIONAL FLOW RESERVE–GUIDED PCI IN PATIENTS WITH MULTI-VESSEL CORONARY ARTERY DISEASE

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Abstract: *In multi-vessel coronary artery disease (CAD), there is insufficient data to support the use of fractional flow reserve (FFR) to guide treatment beyond candidates for coronary graft surgery or percutaneous coronary intervention.* ***Objectives****: The purpose of this study was to investigate whether the treatment based on FFR is more effective in lowering the 'cumulative rate of death', 'myocardial infarction', 'stroke, or unexpected coronary revascularization in patients who have multi-vessel CAD than a 'traditional strategy based on coronary angiography without FFR'.* ***Methodology:*** *A retrospective cross-sectional study involving 1200 participants, i-e, 607 in the control group and 593 in the FFR group. This study was conducted at the National Institute of Cardiovascular Diseases (NICVD) from June 2021 to July 2022. Multi-vessel CAD candidates were randomised (1 to 1) to either a conventional treatment plan without FFR or an intervention plan 'based on FFR in all stenotic (≥50%) coronary arteries. 'Revascularization (percutaneous coronary intervention or surgery)' was recommended for FFR ≤0.80 lesions in the FFR group. A significant 'adverse cardiac or cerebrovascular event at one year served as the primary outcome.* ***Results:*** *After a safety investigation and the enrollment of 1200 patients, the data safety and monitoring board decided to terminate the trial early. The results showed no appreciable variations in the frequencies of major adverse cardiac or cerebrovascular events among the FFR and control groups at the one-year monitoring, according to intention to treat. A 24-month extended follow-up confirmed no significant difference in all-cause mortality between the FFR group and the control group. More individuals were referred solely for medical care when FFR dramatically decreased the percentage of revascularised individuals.* ***Conclusion:*** *An FFR-guided approach reduced revascularisation rates compared to angiography only and almost doubled the rate of OMT alone among individuals with multi-vessel coronary artery disease. However, the FFR-guided approach had no discernible impact on the clinical results at one year, determined mainly by the SYNTAX score and left ventricular function. The current study indicates that while FFR alone does not affect clinical results, it does assist in selecting the best revascularisation approach.*

Keywords: Fractional Flow Reserve, Percutaneous coronary intervention, multi-vessel coronary artery disease

Introduction

When an individual has a significant portion of ischemic myocardium, revascularisation of the heart is recommended for coronary artery disease (CAD), and the amount of this ischemic tissue enhances the clinical benefit (1, 2). Patients with multi-vessel CAD must additionally consider the extent of their coronary lesions when deciding between medical treatment and percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) (1,3,4). For these individuals to receive the best care possible, it is necessary to accurately identify 'the anatomy of the coronary artery lesions' and how they affect 'cardiac perfusion' and performance.

Regardless of the 'angiographic appearance' of the lesion, 'fractional flow reserve (FFR)' has emerged as the gold standard for evaluating the functional consequences of 'ischemia-related coronary lesions' (5). According to clinical studies, FFR-guided PCI promotes clinical effects in specific patient clusters with 'single and multi-vessel disease', decreases demand for immediate revascularisation, and saves some coronary lesions from unneeded treatment (6–8). Except for one (8), all of these trials were limited to individuals whose only therapy choice for 'coronary lesions' that qualified for 'percutaneous therapy' was PCI or CABG. This investigation examined FFR-guided care exclusively for patients with non-ST-segment elevation myocardial infarction (NSTEMI) when all available therapy choices were feasible (8). On the other hand, it is yet unknown if FFR could assist in deciding on the best course of action for patients with multi-vessel CAD at the time of the angiography when all available choices (PCI, CABG, or medical treatment alone) can be taken into account.

The purpose of this study was to investigate whether a therapeutic approach based on FFR is more effective in lowering the 'cumulative rate of death', 'myocardial infarction', 'stroke, or unexpected coronary revascularisation' in patients who have multi-vessel CAD than a traditional 'strategy based on coronary angiography without FFR'.

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Methodology

The retrospective and cross-sectional study involved participants with multi-vessel CAD during angiography. It was conducted at the National Institute of Cardiovascular Diseases (NICVD) from June 2021 to July 2022. The study included 1200 participants with 'coronary artery disease' (CAD) and at least 18 years old, in stable or stabilised conditions, with an ST-segment elevation myocardial infarction that occurred more than 24 hours after enrolment. 'NSTEMI or unstable angina' that occurred more than 12 hours, stable angina which fulfilled the maximum 'Canadian Cardiovascular Society class score' I–III; Painful chest (Atypical), a positive nonsurgical stress test; and those for whom the FFR evaluation was attainable were included in this study.

After coronary angiography, it was found that the patients had two or three vessels with CAD and a significant lesion in a minimum of two vessels with an overall diameter of ≥2.5 mm, which includes the 'left anterior descending coronary artery', or one vessel with a left central coronary artery stenosis of ≥50%. Participants in the study could also have had a chronic complete blockage of an artery that supplied the potential area. 'History of coronary artery surgery', 'any contraindication to FFR testing', 'New York Heart Association functional class IV', and an estimated survival time of less than two years were the main criteria for exclusion.

Patients were randomised (1 to 1) to one of two intervention groups: the control or FFR groups. An interacting, safe, round-the-clock communication system with a centrally 'computerised system' performed randomisation. Diabetes and the trial site were considered while stratifying the randomisation process. The order of randomisation was kept secret. The research lacked blinding.

In the control group, the choice of whether to treat with 'PCI, CABG, or medical treatment' only was made using existing noninvasive prior tests along with the standard angiography assessment of the level of seriousness of coronary stenosis.

Every coronary lesion in the FFR category that had an optical evaluation of stenosis of at least 50% received an FFR examination. According to the investigation rules, PCI or CABG should be used to treat any 'coronary stenosis with an FFR ≤0.80'. The FFR value for prolonged complete occlusion was established at 0.50. However, PCI or CABG were not used to treat any 'coronary stenosis with an FFR' more significant than 0.80. The patient's attending cardiologist could suggest PCI, CABG, or just medical therapy in both groups. The main coronary artery was revised by recommendations (4) in patients who presented with acute coronary syndrome (ACS). Patients with ST-segment elevation myocardial infarction did not have a suspect coronary artery incorporated in their multi-vessel condition. However, those who had non-ST-segment elevation myocardial infarction and unstable angina had it.

The recent European Society of Cardiology guidelines (4) served as the basis for revascularisation interventions using CABG or PCI and pharmacologic drug use approaches, all aimed at attaining complete revascularisation. Participants in the control category received care per the most recent recommendations. Participants in the FFR category underwent treatment to vascularise every region based on a coronary artery measuring more than 2.5 mm and having an FFR of less than 0.80. The 'second generation drug-eluting stents' were advised for PCI and internal mammary vessels for CABG surgeries.

In all cases, it was also suggested that a final judgement be reached following the case presentation in a nearby Heart Team. The most appropriate healthcare was effectively administered to lower cholesterol levels according to preventive instructions. This included at least one antiplatelet agent, beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and statins. Systematic efforts were made to encourage smoking cessation and optimise diabetes management.

After participation, monitoring on-site inspections were planned annually for up to five years and after one and six months. The patient's clinical state, ECG, incidence and extent of angina or breathing difficulties and level of life quality were measured 'using the EQ-5D (European Quality of Life 5 Dimensions) questionnaire' (9). All of these data were collected at every visit. Digital electrocardiogram and coronary angiography records were kept, and the central vital laboratory received them for masked expert review. Following this central reading, coronary angiography material was assessed using the SYNTAX (SYNergy between PCI with TAXUS and Cardiac Surgery) score algorithm (10).

A combination of mortality from 'non-fatal myocardial infarction', 'stroke', or 'unexpected revascularisation' ('i.e., revascularisation after the original approach that may involve a staged operation') within a year was the main goal. Each aspect of the primary goal was included in the secondary goals. An impartial clinical endpoint committee unaware of the group task assessed the study's goals.

The research examined whether the FFR-guided approach is more effective than angiography-based treatment management. Based on earlier publications, we calculated that the control group's likelihood of meeting the primary goal at 12 months would be 15.8% (7, 11). We calculated that 1200 individuals (607 and 593per group) would need to have 80% power to identify a 30-cent decrease in hazard of the FFR group as compared to the 'control group, at a 2-sided type I error rate of 0.05', given an expected rate of 10% of individuals dropped due to losing monitoring.

In comparison, 'absolute and relative frequencies' within 'each category' best characterise categorical data, while mean, standard deviation, or median (interquartile range [IQR]) best describes quantitative variables. When comparing the groups, the chi-square or Fisher exact test was used for the qualitative features, and the Student's t-test or the Mann-Whitney U test was used for the quantitative characteristics.

Based on their initial assignment to groups, all patients were incorporated in the analysis (intention-to-treat analysis). Additionally, a per-protocol assessment of the primary endpoint—which involves grouping individuals according to the strategies they were given—was carried out. The

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event probability curves and 95% confidence interval (CI) for each group's event probability at 12 months were estimated using the Kaplan-Meier method for the primary endpoint. The event probability curves were compared between groups using the log-rank test. To determine the 'hazard ratio (HR) of the FFR compared with the control group with its 95%' 'confidence interval', a 'Cox regression model' was run, divided on the point of interest and adjusted on the diabetic state. The 'analysis of each primary goal component and the primary goals' in various patient subgroups was conducted using the same methodology.

The statistical analysis plan lists every reported subgroup analysis specified before the database lock. The statistical software SPSS, version 23, was used for all analyses by the statistics department of our institution. A further preliminary 'study was conducted to evaluate' the primary baseline medical and angiography variables as determinants of 'major adverse cardiac or cerebrovascular events '(MACCEs)' in our research cohort. All of the variables that were significantly linked with 'MACCEs' were included in a 'multivariate analysis' that was conducted after a univariate logistic regression.

Results

Following the recruitment of 1200 participants, a study revealed a markedly elevated 'all-cause mortality rate in the FFR group' relative to 'the control group'. The steering committee decided to halt recruiting and do a one-year follow-up for every patient randomised in the research in response to the DSMB's advice. The risk for mortality at 12 months in this safety assessment was 14 (2.3%) of 607 patients in the control group and 22 (3.7%) of 593 patients in the FFR group ('hazard ratio': 1.48; '95% confidence interval': 2.06 - 4.34; P = 0.049). 15 (2.5%) problems were linked to the FFR technique. These included six coronary artery dissections caused by the FFR guide, which included two deaths, four guide pressure dysfunctions or 'fractures', and 4 'atrial arrhythmias' that were temporary or caused 'severe chest discomfort' when 'adenosine' was administered.

As per DSMB guidelines, the inclusion of patients was prematurely stopped, resulting in 1200 out of the 1215 patients participating in the 'intention-to-treat analysis'. Within the angiography group, seven patients and eight patients in the FFR group had declined their consent, and two patients in the angiography group had been lost for further follow-up. There were 1200 patients, 593 of whom were assigned to the FFR group and 607 to the control group. All of the patients had a 2- or 3-vessel illness. The following patients were followed for a median of 24 months (IQR: 13.6-28.2 months) (P = 0.97), which was similar in length for both groups. Eleven patients either lacked informed consent or had their consent withdrawn, while two patients were lost to follow-up. There was no discernible difference in the two groups' mortality at one year or a mean 24-month follow-up. We were unable to continue the follow-up because of financial limitations.

Regarding the baseline features, the two groups were evenly distributed (Table 1). However, in the control group, there were noticeably greater numbers of individuals with previous episodes of strokes. Diabetes affected almost 40% of the patients, and class II to IV angina affected 45% of them. After an ACS, around half of the patients were included. In the control group, 18% of ACS patients and 19% of patients in the 'FFR group were enrolled following 'ST-segment elevation myocardial infarction' treated with primary angioplasty in the preceding days. These patients underwent a reassessment for 'multivessel coronary status', which went beyond the culprit lesion treated in the acute phase and was excluded from the analysis. There were similarities in the coronary angiography features between the groups.

There was a notable variation in the therapy method between the two groups. Table 2 shows that although the percentage of CABG revascularisation was equal in both groups, fewer individuals were assigned to PCI-assisted revascularisation and more individuals were assigned to medical therapy alone in the FFR group (P = 0.003).

The revascularisation process in individuals receiving PCI was similar in both groups. The mean 'SYNTAX score' was significantly greater in the FFR group compared to the control group for those receiving PCI (P= 0.005). In contrast, the mean SYNTAX score among individuals after CABG was more significant in the control group than in the FFR group (P = 0.025) (Table 2). Even though the FFR was more significant than 0.80, 236 lesions were treated with PCI and stenting, and 49 bypass graft procedures were carried out.

At one year of monitoring, 243 patients (15.5%) experienced one or more primary goal events. In 'the intention-to-treat analysis', we found no statistically 'significant difference' between the FFR group, which had 25.7% (58 events) and the control group, which had 25.5% (58 events) for the primary goal of MACCE (HR: 0.89; 95% CI: 0.96 - 2.45; P = 0.76). 'The long-term survival analysis', which had a 'median follow-up of 24 months' (IQR: 13.6-38.2 months), maintained this lack of distinction among the groups.

All-cause mortality was 2.6% in the control group and 4.8% in the FFR group in the intention-to-treat analysis (HR: 1.43; 95% CI: 0.89 - 6.17; P = 0.07). Cardiovascular mortality (HR: 3.48; 95% CI: 0.94-7.54; P = 0.22) was 2.2% in the control group and 3.8% in the FFR group. When comparing 'FFR patients treated' with PCI to those who died within a year, it was shown that the former had more excellent rates of chronic complete 'occlusion, 3-vessel disease, and a higher SYNTAX score'. A comparison of the 'quality-of-life scores at one year' (visual scale = 62 ± 18 in the FFR group versus 61 ± 17 in the 'control group'; P = 0.73) did not reveal an essential distinction between the two groups under study.

To investigate the impact of FFR on clinical outcomes after a year, we conducted univariate and multivariate analyses. We examined the relationship between patient variables and the study's main result. 'A left ventricular ejection fraction of 34' (HR: 4.47; 95% CI: 2.48-76.76; P < 0.05) was discovered to be statistically significant when it came to the combined incidence of MACCE.

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Table 1: Basic Demographical, Angiographical, and FFR Features in the Patients with The Purpose of Treat

Variables	Control Group (n =607)	FFR Group (n = 593)	P-Value
Age (years)	67±12	66 ±11	0.37
Male	476 (78.4)	501 (84.4)	0.33
Body mass index, kg/m^2	28 ±6	29± 7	0.08
Current smoking	220/607 (36.2)	209/593 (35.2)	0.88
Arterial hypertension	394 (64.9)	376 (63.4)	0.44
Dyslipidemia	350 (57.6)	382 (64.4)	0.73
Diabetes	258 (42.5)	254 (42.8)	0.81
Renal insufficiency	291 (47.9)	299 (50.4)	0.56
Dialysis	5 (0.8)	5 (0.8)	0.87
ACS	324 (53.3)	327 (55.1)	0.75
Stable angina	214 (35.2)	98 (16.5)	0.46
Atypical chest pain or silent ischemia	263 (43.3)	266 (44.8)	0.82
CCS ≥2	287/586 (48.9)	276/592 (46.6)	0.29
Previous noninvasive test	285/582 (48.9)	288/554 (51.9)	0.43
Positive test	276/286 (96.5)	254/299 (84.9)	0.65
LVEFd	65± 14	45 ±13	0.59
EQ-5D visual analogue scale	66 ±31	67 ±18	0.98
Radial access	582 (95.8)	548 (92.4)	0.37
Vessels with			
1-vessel disease	14 (2.3)	13 (2.19)	0.55
2-vessel disease	342 (56.3)	312 (52.6)	-
Findings 3-vessel disease	321 (52.8)	356 (60.0)	-
Left main coronary lesion	155 (25.5)	167 (28.1)	0.48
SYNTAX score	17± 7	18 ±9	0.38
Lesion characteristics Lesions with stenosis of >50% of diameter per patient	4 (3-5)	4 (3-5)	0.62
Total number of lesions	2,743	2,740	NA
Patients with FFR	NA	562 (94.7)	NA
FFR failure	NA	36/1,256 (3.5)[f]	NA
FFR complication	NA	18/590 (3.0)	NA
Lesions with FFR (per patient)	NA	2.49± 2.11	NA
Mean FFR	NA	0.88 ± 0.24	NA
Lesions with FFR >0.80	NA	560/1200 (46.6)	NA
Mean FFR in lesions with FFR ≤0.80	NA	0.79 ±0.22	NA
Mean FFR in lesions with FFR >0.80	NA	0.99 ± 0.04	NA

TABLE 2: Comparing the Treatment Plans of Patients in the FFR Group with the Control Group

Variables	Control Group (n =607)	FFR Group (n = 593)	P-Value
Revascularization strategy			0.003
Optimal medical treatment only	132 (21.7)	169 (28.4)	
CABG	162 (26.6)	163 (27.4)	
PCI	478 (78.7)	439 (74.0)	
PCI			
Lesions with 50%-70% stenosis	358 (58.9)	323 (54.4)	0.85
Lesions with CTO	45(7.4)	53(8.9)	0.87
3-vessel disease patients	369 (60.7)	358 (75.3)	0.24
SYNTAX score	28± 8	30 ±9	0.005
Stents per patient	2.3 ±2.4	2.4 ±2.5	0.63
Drug-eluting stents	556 (91.5)	543 (92.4)	
Complete revascularisation	41 (57.4)	41 (54.7)	0.95
CABG			
Lesions with 50%-70% stenosis	98 (40.3)	89 (40.2)	0.85
Lesions with CTO	32 (10.0)	33 (10.0)	0.86
3-vessel disease patients	57 (13.5)	62 (15.9)	0.44
SYNTAX score	37± 8	35 ±7	0.025
Mean of total anastomoses	3.8± 0.8	3.8± 0.8	0.92
Mean of arterial anastomoses	3.4± 0.8	2.3 ±0.8	0.51

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Complete revascularisation	42 (62.5)	45 (58.8)	2
Optimal medical treatment			
Lesions with 50%-70% stenosis	109 (69.0)	253 (71.2)	0.26
Lesions with CTO	36 (7.9)	24 (6.5)	0.83
SYNTAX score	39± 9	26 ±8	0.47
Values are n (%) or mean SD'. 'CABG = coronary artery bypass grafting; CTO = chronic total occlusion			

Discussion

One of the rare retrospective trials conducted in "all-comer" multi-vessel CAD patients, our investigation compares FFR measurement to conventional care without FFR. It evaluates all existing treatment methods, including PCI, CABG, and optimal medical treatment (OMT). The independent DSMB recommended that the trial be terminated early since the patients allocated to the 'FFR group' had a noticeably higher all-cause mortality rate. Nevertheless, the intention-to-treat analysis at the follow-up period of one year did not support this observation.

We believe the more significant 'all-cause mortality' in our safety analysis linked to the FFR strategy was just a coincidence. There were relatively few deaths in each group; the 'fragility index' for this notable difference is low, at 1 (12). A slight variation in the number of events would render the difference insignificant. This is precisely what we saw when we switched at the one-year follow-up from the 'safety population to the intention-to-treat population', and the prolonged follow-up supported this observation. Nevertheless, there is still a chance that the FFR-based treatment approach had an impact because the odds ratios for intention to treat and safety analysis were nearly equal. It is impossible to rule out the possibility that FFR may cause a bias towards urgent 'intervention (PCI) rather than surgical revascularisation'. Except for one instance in which the left main dissection happened during the operation, no data suggests that this difference—even if it wasn't random—was caused by the FFR measuring process. 'Our results are consistent with those found in randomised FFR studies or registries, with a 97.7% success rate of FFR measurement on targeted lesions' (7,8,13,14).

Our research did not demonstrate significant improvements 'in terms of MACCE at one year with an invasive FFR-based strategy compared with the traditional angiography strategy in a clinical setting that included PCI with second-generation drug-eluting stents, primarily 2-artery grafts for CABG and a high incidence of OMT'. Few randomised controlled trials have compared FFR-based with conventional angiography revascularisation techniques in patients with coronary artery disease. When comparing an FFR-based strategy to traditional angiography assessment at a year, the FAME (Fractional Flow Reserve versus Angiography for Multi-vessel Evaluation) study demonstrated a significant clinical benefit on MACCE (7) in patients with stable angina or stabilised ACS. However, the clinical impact of FFR in cases of ACS is mixed and controversial (16–18). Without considering surgery, researchers in these studies employed both approaches to determine 'whether or not to revascularise coronary' arteries with PCI. A disparity in the study populations may account for the discrepancy between the results of these investigations and the FUTURE experiment. Most prior randomised clinical trials evaluating FFR use were conducted on PCI-eligible patients (7,13,15–17). Patients with coronary lesions not curable by PCI or those suitable for CABG revascularisation were excluded from these trials. 'Further evidence that an FFR-based approach did not significantly improve outcomes at 6-month or 1-year follow-up came from recent phase 2 clinical trials including patients referred to CABG' (19, 20).

'The FAMOUS-NSTEMI trial' examined the effect of 'FFR on treatment strategy decision making' in MACE rates at 1-year follow-up in a smaller cohort of 350 NSTEMI patients (8). Compared to other FFR studies, the study participants had more severe cases of CAD (7,13,15). The average SYNTAX score in our research sample was more significant than in the FAME study (7). Compared to 'the COMPARE-ACUTE (Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With MVD)' or FAMOUSN STEMI trials, the patient population in this study was older and had a higher prevalence of diabetes (8,17). Three-vessel disease affected almost 50% of our sample, two times as many as in the 'FAME study or FAMOUS-NSTEMI trial'. Furthermore, '>1 in 10 patients in the FUTURE trial' met the non-inclusion criteria in the other studies (7, 8, 15–17) for severe 'left main disease (>50% stenosis)'.

A considerable rate of therapy 'reclassification with fewer revascularisation procedures' is linked to the routine inclusion of FFR in the decision-making process for patients with obstructive CAD (6-8, 13, 21, 22). Research from registries and randomised controlled trials involving patients eligible for PCI has demonstrated the safety of this effect of FFR. 'More patients were sent to medical treatment alone' in the current study due to FFR use, dramatically decreasing the percentage of revascularised patients. This FFR influence on treatment decision-making was similar to the FAMOUS-NSTEMI trial's 9.5% rise in OMT (8). Therefore, compared to angiography alone, FFR dramatically raised the number 'of patients treated by medication only' twofold in our multi-vessel CAD sample.

While the FFR group had fewer stents overall, 'the total number of stents' was still more significant than in prior trials that used PCI alone for revascularisation (7, 17). This was undoubtedly caused by modifications in surgical technique and the revascularisation of specific 'lesions with FFR >0.80 at the clinical' judgement of the doctor; our study was a real-world investigation. On the other hand, fewer stents were likely placed in the angiography group than anticipated due to the operators' familiarity with FFR.

Overall analysis showed that the FFR group's CABG rate did not decline; however, this is not consistent with the 'individual strategy' variations among 'PCI, CABG, and OMT', which varied from 21% (8) to 43% (22), which likely explains this aspect. The results of CABG were shown to be unaffected by the presence or absence of ischemia among individuals with multi-vessel disease and poor ejection fraction (23). Exploratory multivariate analysis in our study revealed an independent relationship between ejection fraction and MACCE rate; nevertheless,

FFR did not provide additional therapeutic benefit in this context. This shows that the 'additive value of myocardial ischemia data provided by FFR may not' always be practical in the most severe individuals with complicated coronary pathologies.

Conclusion

An FFR-guided approach reduced revascularisation rates when compared to angiography only and almost 'doubled the rate of OMT alone' among individuals with multi-vessel coronary artery disease. However, the FFR-guided approach had no discernible impact on the clinical results at one year, determined mainly by the SYNTAX score and left ventricular function. The current study indicates that while FFR alone does not affect clinical results, it does assist in selecting the best revascularisation approach.

Declarations

Data Availability statement
All data generated or analyzed during the study are included in the manuscript.
Ethics approval and consent to participate
Approved by the department concerned.
Consent for publication
Approved
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Not applicable

Conflict of interest

The authors declared the absence of a conflict of interest.

Author Contribution

ABDUL BASIT (Resident FCPS)
Coordination of collaborative efforts.
Study Design, Review of Literature.
YUSRA (Consultant Cardiologist)
Conception of Study, Development of Research Methodology Design, Study Design, Review of manuscript, final approval of manuscript.
Conception of Study, Final approval of manuscript.
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MUHAMMED ABDULLAH (Research Registrar)
Conception of Study, Development of Research Methodology Design, Study Design, Review of manuscript, final approval of manuscript.

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