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Fractional flow reserve in acute coronary syndromes and in stable ischemic heart disease: clinical implications☆

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ABSTRACT

Background: Fractional Flow Reserve (FFR) in Stable Ischemic Heart Disease (SIHD) is universally accepted, while in Acute Coronary Syndromes (ACS) is less established.
Aims of this retrospective study were: to compare in patients undergoing FFR assessment the prognostic impact of ACS vs SIHD, to evaluate the clinical relevance of the modality of utilization and timing of FFR assessment and to assess the different outcomes associated with an FFR> or ≤0.80.
Methods: Major cardiac adverse events were assessed at a follow up of 16.4 ± 10.5 months in 543 patients with SIHD and 231 with ACS needing functional evaluation. FFR was used for lesions of ambiguous significance in the absence of a clear culprit vessel (first intention, FI) and for incidental lesions in the presence of a clear culprit vessel (second intention, SI). The decision to perform FFR and the identification of the stenosis needing functional assessment were left to the operator's discretion. Revascularization was performed when FFR was ≤0.80.
Results: SIHD and ACS patients were not significantly different for principal clinical characteristics.
ACS patients had significantly more events than SIHD, due to an excess of death and myocardial infarction. This was confirmed when FFR was used as FI, in particular if FFR was >0.80. On the contrary, when FFR was used as SI, event rates were similar between ACS and SIHD patients, regardless of FFR value.
Conclusions: Our study shows that using FFR the risk of recurrent events in ACS is significantly higher than in SIHD. This different outcome is confined to those patients in whom FFR is utilized for lesions of ambiguous significance in the absence of a clear culprit vessel.

1. Introduction

The role of the functional evaluation of the severity of angiographically intermediate stenosis using Fractional Flow Reserve (FFR) in patients with Stable Ischemic Heart Disease (SIHD) [1] is universally recognized and supported by a large number of clinical trials [2,3]. In contrast, its role in Acute Coronary Syndromes (ACS) is still unclear. In this setting, microvascular dysfunction, impairing ability to reach maximal hyperaemia, and the intrinsically dynamic nature of epicardial coronary stenosis could affect an accurate FFR calculation, by overestimating its value [4–7].

A large matter of debate exists on the ability to safely defer revascularization of lesions with FFR value >0.80 and on the correct timing for the functional evaluation in ACS patients. In particular, while the use of FFR as second intention for incidental lesions in the presence of a clear culprit vessel (SI) is generally accepted, it is unclear whether FFR can be performed safely and accurately also as first intention in the absence of a clear culprit vessel (FI).

Considering this background, aims of the present study were the following 1) to compare in patients undergoing FFR assessment the prognostic impact of a diagnosis of ACS vs SIHD 2) to evaluate the clinical relevance of the modality of utilization and timing of FFR assessment 3) to assess the different outcomes associated with an FFR> or ≤0.80.

Abbreviations: ACE, angiotensin-converting-enzyme; ACS, acute coronary syndromes; ARB, angiotensin II-receptor blocker; CABG, coronary artery bypass grafting; CAD, coronary artery disease; FFR, fractional flow reserve; FI, first intention; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events; NSTE-ACS, non-ST elevation acute coronary syndromes; NSTEMI, non-ST segment elevation myocardial infarction; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; SI, second intention; SIHD, stable ischemic heart disease; STEMI, ST segment elevation myocardial infarction; TVR, target vessel revascularization; UA, unstable angina.

☆ The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. They have not conflict of interest to declare.

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2. Methods

We performed a retrospective analysis of all consecutive patients with ACS or SIHD evaluated by FFR in our institution from 1st January 2012 to 31th of December 2016. ACS was defined in presence of a clinical diagnosis of ST segment elevation acute myocardial infarction (STEMI), non-ST segment elevation acute myocardial infarction (NSTEMI) and Unstable Angina (UA) according to European Guidelines [8,9]; NSTEMI and UA patients were considered as having non-ST segment elevation ACS (NSTE-ACS). SIHD patients comprised patients with chronic stable angina, silent ischemia or with chest pain in the presence of high pre-test probability of coronary artery disease. ACS patients were relatively stable, without signs of hemodynamic or electric instability at the time of invasive functional assessment. The decision to perform FFR and the identification of the stenosis needing functional assessment were left to the operator's discretion. Surgical or percutaneous revascularization was performed when FFR was ≤0.80. Clinical exclusion criteria were severe valvular heart disease, severe acute heart failure and significant comorbidities limiting life expectancy to less than 1 year. Diagnostic coronary angiography was performed using radial or femoral approach using Iomeprol (Iomeron 350®, Bracco Imaging, Milan, Italy) as non-ionic radiographic contrast medium. The local Ethics Committee of the Fondazione Policlinico Universitario Agostino Gemelli approved the study.

2.1. Functional assessment

Functional assessment was performed as previously described [10]. In brief, a 0.014-inch pressure monitoring guide-wire (Certus or Aeris Pressure Wire, Saint Jude Medical, Minnesota, USA; Primewire or Verrata wires, Volcano Corporation, San Diego, California, USA) was calibrated and introduced into the guiding catheter. The pressure transducer was advanced just outside the tip of the guiding catheter, and the pressure measured by the sensor was then equalized to that of the guiding catheter. Then pressure wire was advanced distal to the lesion to be evaluated. Hyperaemia was obtained using intravenous or intracoronary adenosine [11] or contrast medium according to a validated protocol [12]. An FFR value of ≤0.80 was considered the significant ischemic threshold.

2.2. Data collection and endpoints

All patients functionally assessed using a pressure wire were entered in a dedicated database and were allocated to 2 groups according to the utilization of FFR for lesions of ambiguous significance in the absence of a clear culprit vessel (first intention, FI) or for incidental lesions in the presence of a clear culprit vessel (second intention, SI). The initial patient visit was used to record demographic data, cardiovascular symptoms, and baseline cardiac risk factors. Clinical follow up was obtained by phone or in an outpatient visit. The primary endpoint was a composite of death for any cause, myocardial infarction and clinically driven revascularization. Secondary endpoints were the individual component of the primary composite endpoint. MI was defined as a clinical syndrome characterized by myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia; i.e. detection of a rise and/or fall cardiac troponin with at least one value above the 99th percentile upper reference limit with at least one of the following features: symptoms of ischaemia or new/presumed new significant ST-segment–T wave changes or new left bundle branch block or development of pathological Q waves in the ECG or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality or identification of an intracoronary thrombus by angiography or autopsy. In addition, cardiac death (defined as death due to any cardiac cause, including fatal MI, sudden death with or without documented arrhythmia without known cause, or congestive heart failure) and target vessel revascularization (TVR, defined as subsequent revascularization of the index vessel by either PCI or bypass grafting of the target vessel) were also registered. Three independent reviewers (blinded to the angiographic/FFR and demographic data) adjudicated the cause of death through chart review, death certificate, and physicians' records.

2.3. Statistical analysis

Categorical variables were expressed as percentages and analysed by Fisher exact test. Continuous variables were expressed as mean ± SD and/or median [interquartile range] and compared using the paired *t*-test or the nonparametric Wilcoxon test, as appropriate. Kaplan Meier curves were constructed for the primary endpoint and its components, and then compared using a Log-rank analysis. Moreover, we performed a separate analysis according to a landmark point 1 year after the enrolment. A Cox regression analysis, including as covariates age, sex, LVEF, diabetes, dyslipidaemia and smoking habit, was performed in order to test the effect of a diagnosis of ACS vs SIHD and of FFR. Differences were considered significant with $p < 0.05$.

3. Results

3.1. General findings

A total of 863 patients underwent functional assessment using pressure wire in 1004 ambiguous stenosis. Eighty-nine patients were excluded for severe heart failure (34), severe valvular heart disease needing surgical or interventional treatment (45) and life expectancy lower than 1 year for non-cardiac reasons (10). In the remaining population, 543 patients had a diagnosis of SIHD and 231 of ACS, including 50 STEMI and 181 NSTE-ACS (114 NSTEMI and 67 UA). This was the population of the present study.

A total of 636 lesions in patients with SIHD and of 273 in ACS patients (50 STEMI with 54 lesions, 117 NSTEMI with 133 lesions, 64 UA with 86 lesions) were functionally assessed. FI FFR was used in 453 patients with SIHD and in 130 patients with ACS; SI FFR was used in 90 patients with SIHD and in 101 patients with ACS. SI FFR in NSTE-ACS was performed during the index procedure after treatment of the culprit lesion in 35 patients and in a staged manner in 16 patients. In patients with STEMI, SI FFR was performed at least 3 days after primary PCI. Patients with ACS and with SIHD did not differ significantly except for a higher prevalence of males and smoking habit and, as expected, for a more aggressive medical therapy at time of functional assessment in ACS, especially regarding dual antiplatelet therapy (Table 1). At least 1 FFR was positive in 178 SIHD (32.7%) and in 88 ACS patients (38.1%). In 20 cases (7 in ACS: 1 STEMI, 3 NSTEMI, 3 UA) >1 lesion had an FFR value ≤0.80. In all patients with FFR value ≤0.80 revascularization was performed percutaneously except for 51 patients who underwent coronary artery bypass grafting, using arterial and venous conduits, for a significant multi-vessel disease involving left main or proximal left anterior descending (33 in SIHD and 18 in ACS).

Mean follow up was 16.4 ± 10.5 months and was not significantly different between the two groups (Table 1). Patients with ACS had significantly more events at follow up than patients with SIHD (Fig. 1). This was due to an excess of death (mainly cardiac death) and MI observed in patients with ACS compared to those with SIHD, while TVR was not significantly different (Supplemental table 1). Cox regression analysis confirmed that ACS and FFR ≤ 0.80 were associated with a worse prognosis (Supplemental table 2).

3.2. Outcome according to FI FFR vs SI FFR

In the FI FFR subgroup, the outcome was worse in ACS as compared to SIHD patients mainly due to a higher risk of death and MI (Fig. 2A and Supplemental Table 3). This was confirmed also at Cox regression analysis (Supplemental Table 4). A borderline significant difference between ACS and SIHD was evident from the beginning when at least 1 FFR was ≤0.80 (Fig. 3A, Supplemental Table 5), while a significant difference between ACS and SIHD was observed after 1 year when all FFR were >0.80 (Fig. 3B, Supplemental Table 6). This was clearly demonstrated by the 12-month landmark analysis showing a significantly higher incidence of all events in ACS compared to SIHD (Fig. 3B). In contrast, in the SI FFR subgroup event rates were similar between ACS and SIHD patients (Fig. 2B, Supplemental Table 2), both when at least one FFR was ≤0.80 (Supplemental Table 5) and when all FFR were >0.80 (Supplemental Table 6). Notably, in the SI FFR subgroup a non-significantly increased prevalence of three-vessel disease was apparent in SIHD vs ACS patients ($p = 0.10$, data not shown). Cox regression analysis confirmed that in the subgroup of patients in whom FFR was performed as second intention, there was no significant difference in prognosis between those with a diagnosis of SIHD or ACS (Supplemental Table 7). Similar results were obtained excluding patients with STEMI (Supplemental Table 8).

4. Discussion

Our study shows that using an FFR-guided strategy of myocardial revascularization the risk of recurrent events in ACS is significantly higher than in SIHD. This different outcome is confined to those patients in whom FFR was utilized for lesions of ambiguous significance in the absence of a clear culprit vessel.

According to current guidelines [1], FFR is the invasive standard reference in patients with SIHD to prove ischemic threshold of angiographically intermediate epicardial coronary lesions and guide

Table 1
Baseline characteristics of patients.

	All patients ($n = 774$)	SIHD ($n = 543$)	ACS ($n = 231$)	p Value
Age	67.9 ± 10.3	67.9 ± 9.9	68.1 ± 11.1	0.845
Men	571 (73.8%)	387 (71.3%)	184 (79.7%)	0.016
Diabetes	194 (25.1%)	133 (24.5%)	61 (26.4%)	0.587
Hypertension	656 (86.6%)	458 (84.3%)	198 (85.7%)	0.663
Smoking habits	399 (51.6%)	268 (49.4%)	131 (56.7%)	0.071
Dyslipidemia	482 (62.3%)	346 (63.7%)	136 (58.9%)	0.224
Family history of CAD	208 (26.9%)	143 (26.3%)	65 (28.1%)	0.596
Medications				
Aspirin	685 (88.5%)	475 (87.5%)	210 (90.9%)	0.178
P2Y12 inhibitor	450 (58.1%)	301 (55.4%)	189 (81.8%)	0.021
β-blockers	556 (71.8%)	381 (70.2%)	175 (75.8%)	0.117
ACE inhibitor or ARB	527 (68.1%)	360 (66.3%)	167 (72.3%)	0.110
Calcium-channel blockers	113 (14.6%)	86 (15.8%)	27 (11.7%)	0.149
Statin	551 (71.2%)	372 (68.5%)	179 (77.5%)	0.012
Previous myocardial infarction	154 (19.9%)	106 (19.5%)	48 (20.8%)	0.695
Previous PCI or CABG	359 (46.4%)	255 (46.9%)	104 (45%)	0.637
LVEF	55.3 ± 9.0	55.3 ± 9.1	55.2 ± 8.8	0.945
% stenosis visual estimation	56 ± 10%	56. ± 10%	57 ± 10%	0.294
Mean Pd/Pa	0.93 ± 0.05	0.93 ± 0.04	0.92 ± 0.05	0.14
Mean FFR	0.84 ± 0.04	0.84 ± 0.07	0.84 ± 0.07	0.47
Localization of FFR-interrogated lesions	909	636	273	0.48
Left main	39 (4%)	25 (4%)	14 (5%)	
Left anterior descending	529 (58%)	380 (60%)	149 (55%)	
Left circumflex	157(17%)	108 (17%)	49 (18%)	
Right coronary artery	184 (20%)	123 (19%)	61 (22%)	

myocardial revascularization. This is supported by a plethora of different randomized clinical trial [2,3,13] and also confirmed in large "real world registries" [14,15]. In contrast, in ACS patients the role of FFR is still debated. Current European guidelines on STEMI [8] mention FFR only as a part of staged revascularization approach in patients with multivessel disease while those on NSTE-ACS [9] openly discourage the use of FFR asserting that: "The achievement of maximal hyperaemia may be unpredictable in NSTEMI because of the dynamic nature of coronary lesions and the associated acute microvascular dysfunction. As result, fractional flow reserve may be overestimated and the haemodynamic relevance of a coronary stenosis underestimated".

In the subpopulation of the pivotal trial FAME 1 [2,13], comprising patients with stabilized ACS, FFR-guidance led to a better outcome and a significant reduction in costs in comparison to angio-guidance. More recently, in the FAMOUS-NSTEMI trial [16], Layland et al. demonstrated the safety and feasibility of FFR-guidance in patients with recent NSTEMI. In this trial FFR, performed per-protocol in all lesions >30%, cut the rate of coronary revascularizations during index hospitalization compared to angiography. Despite not powered for clinical endpoints, a non-significant trend towards an increased rate of spontaneous MACEs in the FFR-group was observed at 12-month follow-up as compared to the angiography-guided strategy. This called into question the mid-term safety of an FFR-guided revascularization. This concern was

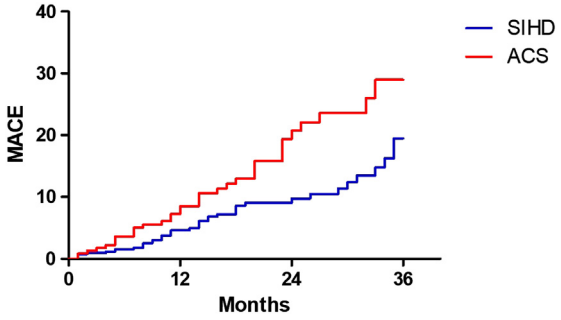

Fig. 1. Kaplan-Meier event curves of the primary composite endpoint (all-cause death, myocardial infarction, clinically-driven revascularization).

confirmed by recent registry data. Indeed, in a large multicenter Italian study Picchi et al. [17] showed that an FFR-guided strategy was associated to a non-negligible rate of target lesion failure (12% at 3 years) mostly driven by a recurrent ACS. This pairs well with our findings showing that a FFR-guided strategy was associated to a MACE rate of about 11%, significantly higher than that in SIHD and especially after 1 year from FFR assessment. Accordingly, Hakeem et al. [18] confirmed that deferring PCI on the basis of non-ischemic FFR in patients with an initial presentation of ACS was associated with significantly worse outcomes than that observed in SIHD, even after a propensity score matching. What are the reasons for this putative lack of safety in deferring? To this regard, it is important to consider the different pathophysiology of stable and unstable coronary lesions and the strong differences between the clinical frameworks that they can determine. Atherothrombotic cardiovascular events are related not only to luminal stenosis severity but also to plaque composition and to the dynamic nature of coronary lesions. This has led to the concept of vulnerable plaque, referring to those lesions more likely to rupture and cause clinical syndromes [19,20]. The functional evaluation of coronary stenosis involved in ACS does not take into account the markers of plaque vulnerability but only the extent of the downstream flow reduction. It is conceivable that intracoronary imaging techniques can provide more information in this setting, also improving the revascularization strategy in these patients. Interestingly, D'Ascenzo et al. [21] recently showed that an OCT approach in ACS patients offers a reduction in target lesion revascularization as compared to an FFR-guided PCI. In the present study, the risk of recurrent events in ACS was significantly higher than in SIHD. This was due to an excess in death and MI observed in patients with ACS compared to those with SIHD, while TVR was not significantly different. Not only the dynamic nature of coronary lesions in ACS but also the clinical features can explain it. A patient with an ACS is by definition a vulnerable patient per se and his prognosis is affected by many factors beyond the hemodynamic features of the culprit stenosis. Our study supports these notions: we found an increased rate of events for ACS in comparison to SIHD patients evaluated as FI by FFR both when FFR was "positive" and when FFR was "negative". This suggests that the ability to guide revascularization strategy, and especially to safely defer revascularization based on a FFR > 0.80, could be weaker in ACS patients compared to SIHD or at least safe only within 1 year of

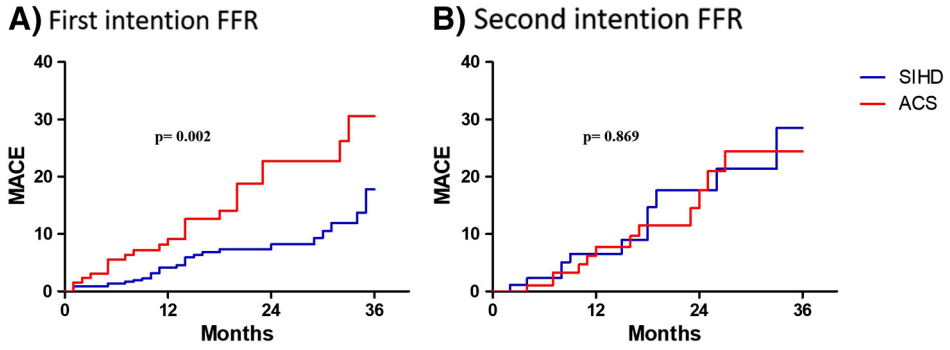

Fig. 2. The primary composite endpoint in SIHD vs ACS when FFR was used as first intention technique (A) or as second intention technique (B).

the acute event. After this time point, a significant higher event rate for ACS vs SIHD patients becomes apparent.

While the use of FFR in the absence of a clear coronary culprit (FI approach) remains questionable, a large body of evidence has been accumulated in recent years on the role of FFR for guiding complete revascularization of non-infarct-related arteries in patients with STEMI and multivessel disease undergoing primary PCI. An in-hospital complete revascularization in the acute setting (during primary PCI in the COMPARE Acute trial [22] and within 2 days in the DANAMI-3-PRIMULTI trial [23]) significantly reduced the risk of subsequent revascularization compared with the treatment of the infarct-related artery only, whereas mortality and reinfarction rates did not differ between the two groups. Despite evidence of a more favourable outcome in patients in whom non-culprit lesions with angiographic diameter stenosis >50% were left untreated based on a non-ischemic FFR value, it should be highlighted that in both studies the competitor of FFR was not angiography or ischemia-driven revascularization but deferral of any procedure, at least during index hospitalization. These findings match well with the current study showing that results of the use of FFR in SI are comparable to those obtained in SIHD in terms of recurrence of MACEs. Although our group [6] showed in patients with NSTEMI undergoing intermediate non-culprit-lesion assessment, a lower reduction in microvascular resistance after moderate doses of intracoronary adenosine compared to patients with stable angina, Ntalianis et al. [5] showed that FFR assessment in NSTE-ACS in the remote territory did not significantly change 1 month after the revascularization of the culprit lesion supporting the possibility to use FFR safely also in the acute and sub-acute setting, at least to guide revascularization of incidental lesions.

4.1. Study limitations

Despite all patients were prospectively enrolled in a dedicated database of all invasive functional assessments of our institution, data were analysed retrospectively, and this has to be acknowledged as a potential limitation of the study. Nevertheless, the quite relevant number of "real world" patients enrolled in the present study can mitigate this limitation and the need to perform multiple sub-analysis to fully characterise the different behaviour of patients with ACS and SIHD assessed by FFR. Another limitation is represented by the fact that choice of the vessel to be interrogated by FFR was left to operator's discretion and mostly driven by angiographic features. This could have led to leave untreated and unassessed a number of potentially relevant (even culprit in some cases) lesions. A recent paper of Van Belle et al. documented that in 38% of all lesions in ACS as well in 39% in SIHD, FFR reclassified severity of stenosis [24]. This means that inaccurate estimation of functional significance of stenosis is very frequent and its consequences potentially important. In fact while patients in whom reclassification occurred had a prognosis comparable to those in whom it didn't, those in whom the information derived from FFR was disregarded, a dire outcome was observed.

In addition, regarding the lack of difference between SIHD and ACS patients in SI, we cannot rule-out the possibility that this subset of SIHD could have a slightly increased risk profile. For example a small, albeit non-significant, increase in the prevalence of 3-vessel disease was observed in SI SIHD patients in comparison to those with ACS.

In the present study, we used FFR only to guide treatment decision. We cannot draw conclusion about the performance of resting indices, such as iFR, that was proposed to have practical advantages over FFR in ACS, especially in the acute setting [25]. Finally, in patients with ACS we cannot dissect the impact of non-cardiac causes of clinical instability from that related to the pathophysiological mechanisms of coronary instability; on the one hand this could have a potential relevance in the reliability of the FFR results and on the other it could affect prognosis regardless of the heart condition. Future studies could be focused to find the best technique (functional assessment, imaging or both) to be employed in the different pathophysiological and clinical conditions.

5. Conclusions

In conclusion, our study suggests that in ACS while an FFR-guided strategy allows to identify non-culprit lesions which deserve

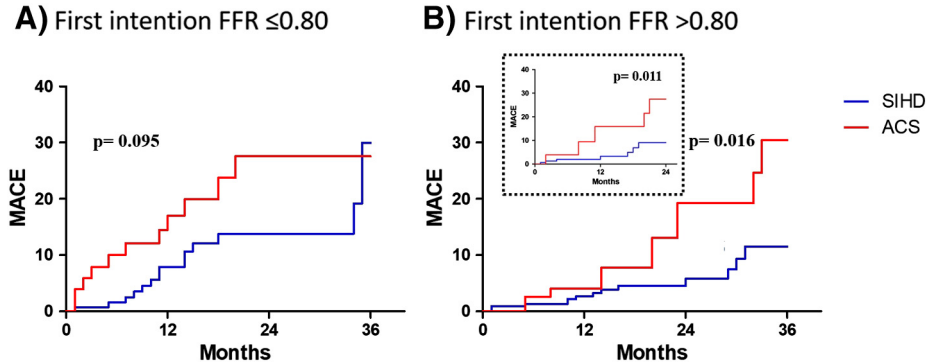

Fig. 3. The primary composite endpoint in SIHD vs ACS when FFR was used as first intention technique and was ≤0.80 (A) or >0.80 (B); in the dotted box the12-month landmark analysis.

revascularization, its use in patients in whom a clear culprit lesion was not recognized and treated, does not allow to reduce the excess risk which characterizes patients with an ACS as compared to patients with SIHD; this support the current guidelines which do not recommend the use FFR in this setting.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.08.024.

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