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Low cerebrovascular event rate in subjects with patent foramen ovale and different clinical presentations
Results from a prospective non randomized study on a population including patients with and without patent foramen ovale closure

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ABSTRACT

Background: There are conflicting data on the role of a patent foramen ovale (PFO) in the pathogenesis of cryptogenic stroke. The aim of this study was to evaluate the incidence of cerebrovascular events associated with PFO in a large population of patients during mid-term follow-up.
Methods and results: We prospectively investigated 446 consecutive patients (58% female, age 50 ± 14 years) in whom PFO was detected by contrast echocardiography following cryptogenic stroke (30.5%), transient ischemic attack (TIA, 23.7%), migraine(10.5%) or evaluation for other cardiac diseases(35%). Prevalence of other clinical conditions potentially associated with cerebral embolism, such as mitral valve disease, atrial fibrillation and aortic atherosclerosis were 31%, 12.5%, 11.2%, respectively; 99 out of 446 patients (22%, group 1) underwent PFO closure, shortly after diagnosis, while 347 (78%, group 2) received only medical therapy (antiplatelet drugs and vitamin K antagonists). During 54 months (range 12–96) of average follow-up few events had been observed: one fatal stroke (1%) in group 1 and 3 nonfatal strokes (0.86%) in group 2 (not significant); there were more TIAs in group 1 than in group 2 (5, 5% versus 3, 0.86%, $p = 0.02$): 8/12 new cerebrovascular events occurred in patients with previous cerebral ischemia and in 7/12 there were other cardioembolic sources. Kaplan–Meier survival free from cerebrovascular events showed a slightly better prognosis in unclosed PFO patients compared to closed PFO ones, statistically significant ($p = 0.004$).
Conclusions: New cerebrovascular events are rare in unselected subjects with PFO, even in those with previous cerebral ischemia and those who have not undergone PFO closure, with an event rate similar to that observed in the general population.

1. Introduction

The etiology of ischemic stroke remains undetermined in up to 40% of patients (pts) affected, despite an extensive diagnostic evaluation. Stroke is referred to as cryptogenic (CS) [1]. A role for patent foramen ovale (PFO) in the pathogenesis of CS, in particular in pts younger than 55 years, has been hypothesized. A statistically significant association between PFO and CS has been reported in several case–control studies, showing a higher prevalence of PFO among stroke pts compared to stroke-free controls [2,3]. Furthermore, a meta-analysis of all case–control reports [4] and a recent large prospective study [5] seem to support this association.

However, a cause–effect relationship between PFO and CS has not been convincingly demonstrated; in particular, the extent of the PFO-related stroke risk in the general population still remains controversial [6]. Furthermore, several studies have consistently found that the presence of a PFO does not inherently increase the risk of recurrent stroke [7–10]. Finally, two large prospective studies recently published showed a very low rate of first cerebrovascular events in asymptomatic subjects with PFO [11,12].

Treatment options for secondary prevention of recurrent stroke in pts with CS and PFO include medical therapy with antiplatelet agents

Abbreviations: ASA, atrial septal aneurysm; CS, cryptogenic stroke; CVEs, cerebrovascular events; IAS, interatrial septum; PFO, patent foramen ovale; TIA, transient ischemic attack.

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or oral anticoagulants, percutaneous device or open surgical closure. The choice of the best therapeutic approach is still a matter of intense debate. The main reason is the lack of published randomized clinical trials comparing the efficacy and safety of percutaneous/surgical closure and those of conventional medical therapy [13]. Given the limited and conflicting data existing in literature, both the American Heart Association/American Stroke Association (AHA/ASA) [14] and the American College of Chest Physicians (ACCP) [15] guidelines recommend antiplatelet therapy for patients with ischemic stroke or transient ischemic attack and PFO (AHA/ASA class IIa, Evidence B; ACCP grade 1A), unless other indications exist for vitamin K antagonist therapy (AHA/ASA class IIa, Evidence C; ACCP grade 1C), and state that PFO closure may only be considered for patients with CS recurrence despite optimal medical therapy (class IIb, evidence C) [14,16].

Accordingly, the aim of the present study was to prospectively evaluate the rate of cerebrovascular events, during a mean follow-up period of 4.5 years, associated with the presence of a PFO in a large population of pts, in whom PFO has been detected, and eventually closed, for different clinical indications.

2. Methods

From January 2000 to January 2008 we prospectively evaluated 446 pts consecutively referred to Echo Lab of Cardiology Division, Spedali Civili Brescia, and Camposanpiero Hospital in whom PFO was detected. Indications for referral were: history of cryptogenic stroke (CS) or transient ischemic attack (TIA), migraine, Doppler-echocardiographic evaluation of other cardiac diseases. The diagnosis of PFO was made by contrast echocardiography in all subjects (see later discussion).

2.1. Echocardiographic evaluation

Transthoracic and transesophageal echocardiographies were performed with commercially available instruments according to standard practice guidelines [17–19]. A PFO was defined as a right-to-left interatrial shunt found during intravenous injection of agitated saline at rest and/or at the end of Valsalva maneuver in all patients. The severity of the shunt was considered mild to moderate or severe on the basis of bubbles number passing through the hole ($\leq$10 versus >10 bubbles, respectively), respectively. Visualization of a "hole" only was not sufficient for diagnosis of PFO. Atrial septal aneurysm (ASA) was defined according to criteria previously published by Agmon et al. [19] and Hanley et al. [20]: 1) diameter of the base of the aneurismal portion of the interatrial septum (IAS) 15 mm or more and either 2) protrusion of the IAS, or part of it, 15 mm or more beyond the plane of the IAS or 3) phasic excursion of the IAS during the cardiorespiratory cycle 15 mm or more in total amplitude. The heart and thoracic aorta were scanned for the presence of potential embolism sources, such as valve or myocardial diseases, thrombus or protruding atherosclerotic plaque [21].

2.2. Assessment of prothrombotic status

Analysis for inherited prothrombotic defects, such as prothrombin G20210A mutation, factor V Leiden G1691A mutation, C protein, S protein and antithrombin III deficiency, was available in 165 subjects $\leq$55 years. Furthermore, in the same patients, the search for thrombophilic conditions, such as connective tissue diseases, antiphospholipid antibody syndrome and lupus erythematosus, was also made. Oral anticoagulant and antiplatelet therapy was recorded.

The therapeutic decisions, either drug therapy alone or combined with PFO closure, based on clinical picture and echocardiographic results, were in charge of Neurologist or Cardiologist or Family Physicians caring for the pts. No author of the present study was actively involved in the decision-making process.

2.3. Follow-up

All patients were followed up prospectively for a mean period of 54 months (range 12 to 96 months) by annual phone call and/or clinical evaluation. Any vascular event or acknowledgment of neurological or cardiac symptoms during the annual standardized interview triggered an in-person assessment. All patients with suspected new cerebrovascular events were clinically examined by a Neurologist and, whenever indicated, underwent an imaging non-invasive study, i.e. brain magnetic resonance imaging or computed tomography.

2.4. Analysis of events

Cerebrovascular events (CVEs) considered were transient ischemic attack, cerebral infarct, or death as the result of the aforementioned conditions. Other events considered were total mortality, cardiovascular events (pulmonary or peripheral embolism, myocardial infarction) and neurologic symptoms not attributed to cerebral ischemia.

All pts gave written informed consent to participate, and Hospital Ethical Committee approved the study.

2.5. Statistical analysis

The demographic and clinical variables were expressed as mean values $\pm$ standard deviation (SD). Mann–Whitney and Chi-square analyses assessed the differences in continuous and in categorical variables, respectively. Survival free from fatal and nonfatal cerebrovascular events for PFO closed and PFO not closed pts was analyzed using Kaplan–Meier cumulative curves. Survival curves were compared using the log-rank test. All analyses were performed using SPSS, version 16.1 software (CHICAGO, IL, USA).

3. Results

3.1. Study population

The demographic, clinical and echocardiographic characteristics of pts included in the study are summarized in Table 1. The most common indication for detection of PFO was represented by recent or remote cerebrovascular events which accounted for more than one half of all pts (54.2%: CS in 30.5% and TIAs in 23.7%), followed by an occasional finding during echocardiographic examination performed for other cardiac diseases in approximately one third (35%) and migraine in the remaining 10.5% of the entire study group. ASA associated with PFO was found in more than one fourth of all pts, and a large right-to-left shunt was relatively common (10.5%). Of interest, clinical conditions potentially associated with cerebral or peripheral embolism, such as mitral valve disease, atrial fibrillation and aortic atherosclerosis were relatively common (Table 1) and several pts showed 2 or more potential causes of cerebral ischemia simultaneously.

Four out of 165 pts $\leq$55 years, in whom prothrombotic status was assessed, had some inherited defects: 2 pts had prothrombin mutation, 1 patient had factor V Leiden Mutation and another 1 had antithrombin deficiency. Some prothrombotic conditions were identified in eight patients: 2 pts had systemic scleroderma, 3 had antiphospholipid antibodies syndrome, 1 patient had lupus erythematosus, another one vasculitis and a third one undifferentiated connective tissue disease.

Table 1
Demographic, clinical and echocardiographic characteristics of study population. See text for details.

	All population
N	446
Sex (M/F)	187/259 (42%/58%)
Age	50 $\pm$ 14 years (15–81)
$\leq$55 years	264 (59%)
Indication to PFO detection	
Cryptogenic stroke	136 (30.5%)
TIA	106 (23.7%)
Migraine	47 (10.5%)
Occasional detection	157 (35%)
Echocardiographic characteristics	
Atrial septal aneurism	117 (26.2%)
PFO tunnel like	21 (4.7%)
Shunt at rest	138 (31%)
Shunt during Valsalva maneuver	299 (67%)
Severe shunt	47 (10.5%)
Associated features	
Thoracic aorta atherosclerosis	50 (11.2%)
Atrial fibrillation	56 (12.5%)
Mitral valve disease	138 (31%)

3.2. Treatment and follow-up

After the result of clinical, laboratory and echocardiographic examinations, antiplatelet drugs or vitamin K antagonists were prescribed from physicians responsible for care of pts to 228 (51%) and 45 (10%) subjects, respectively. Shortly after recognition of PFO, 99 out of 446 pts (22%, group 1) underwent PFO closure, percutaneous [91 pts] or surgical [8 pts], while 347 pts (78%, group 2) only received conventional medical therapy. The clinical indications for closure are indicated in Fig. 1. Only 11 out of 99 pts sent to PFO closure (11%) had a recurrent ischemic event (3 strokes and 8 TIAs), all before initial PFO detection, and, hence, an accepted indication for PFO closure, according to current guidelines [13,14,22,23]. Characteristics of pts with (group 1) and without PFO closure (group 2) are shown in Table 2. Atrial fibrillation was significantly most common in those pts not sent to PFO closure. As expected, echocardiographic indicators of larger PFO, such as shunt at rest and severe shunt, were significantly most common in those pts sent to closure. Furthermore, there was no significant difference in the initial clinical presentation (CS, TIA, migraine or occasional detection) between the two groups.

Mean duration of follow-up was 54 ± 20 months (range 12 to 96 months). The rate of events occurring during follow-up is reported in Table 3. There have been 10 deaths (2.2%) during the follow-up, 1 in group 1 (PFO closed), as a consequence of ischemic stroke, and 9 in group 2 (PFO not closed), due to metastatic cancer (4 pts), cerebral bleeding due to head trauma (1 pt), chronic heart failure (2 pts) and unknown mechanism (2 pts). Regarding cerebrovascular events, 3 nonfatal ischemic strokes (0.86%) were observed in group 2, in addition to one fatal ischemic stroke (1%) in group 1 (difference not significant). Incidence of TIAs was higher in group 1 (5 pts, 5%, versus 3 pts, 0.8%; Table 3). Clinical features of pts with cerebrovascular events are described in Table 4. Of interest, 7 out of 12 pts had one or more abnormalities, such as atrial fibrillation, mitral valve disease or aortic atherosclerosis, potentially responsible for cerebral ischemia, in alternative to PFO.

None of the 4 pts with prothrombotic defects presented a cerebrovascular event during follow-up. Among 8 pts with prothrombotic conditions, only a fifty-eight year old woman, who was affected by lupus erythematosus, on antiplatelet therapy and included in group 2, had recurrent TIAs. Finally, the incidence of other events, such as pulmonary or peripheral embolism, endocarditis and minor aspecific neurologic symptoms, occurred during the follow-up, are presented in Table 3.

Table 2
Demographics, clinical and echocardiographic characteristics by PFO status (closed or not closed).

	Group 1 (PFO closed) $n=99$	Group 2 (PFO not closed) $n=347$	p
Sex (M/F)	46/53 (46.4%/53.6%)	141/206 (40.6%/59.4%)	0.36
Age	47 ± 15 years (15–81)	51 ± 14 years (16–81)	*ns*
≤55 years	66 (66.6%)	198 (57%)	*ns*
Clinical features			
Aortic atherosclerosis	6 (6%)	44 (12.6%)	0.09
Atrial fibrillation	2 (2%)	54 (15.5%)	<0.001
Mitral valvular disease	26 (26%)	112 (32.2%)	*ns*
Echocardiography			
ASA	32 (32%)	85 (24.5%)	*ns*
PFO tunnel like	9 (9%)	12 (3.4%)	0.04
Shunt at rest	51 (51%)	87 (25%)	<0.001
Shunt during Valsalva maneuver	95 (95%)	204 (58.7%)	<0.001
Severe shunt	24 (24%)	23 (6.6%)	<0.001

Fig. 2 shows the Kaplan–Meier analysis of survival free from cerebrovascular events during follow-up: pts without PFO closure showed a statistically significant better prognosis, in comparison to those who underwent PFO closure, i.e. survival at 1, 3 and 5 years: 97.3%, 92.6%, 89.4% in group 1 versus 99.8%, 99.3% 97.8% in group 2, respectively ($p=0.004$).

4. Discussion

The main result of this study, performed on a large population of subjects with PFO, during a mean follow-up of more than four years, indicates a low rate of new cerebrovascular events (fatal and non fatal stroke, TIAs), that is 12 in 446 pts (2.7%), corresponding to a stroke and TIA annual incidence of ~0.2% and ~0.4% respectively. Incidence of cerebrovascular events resulted roughly similar in pts with closed PFO (group 1) and in pts with not closed PFO (group 2). Survival free from cerebrovascular events was higher in group 2 pts (PFO not closed) at Kaplan–Meyer analysis.

Although a statistically significant association between PFO and CS has been demonstrated in the past, mostly through case–control studies showing a higher prevalence of PFO among stroke pts compared to stroke-free controls [2–4], however, a clear cause–effect

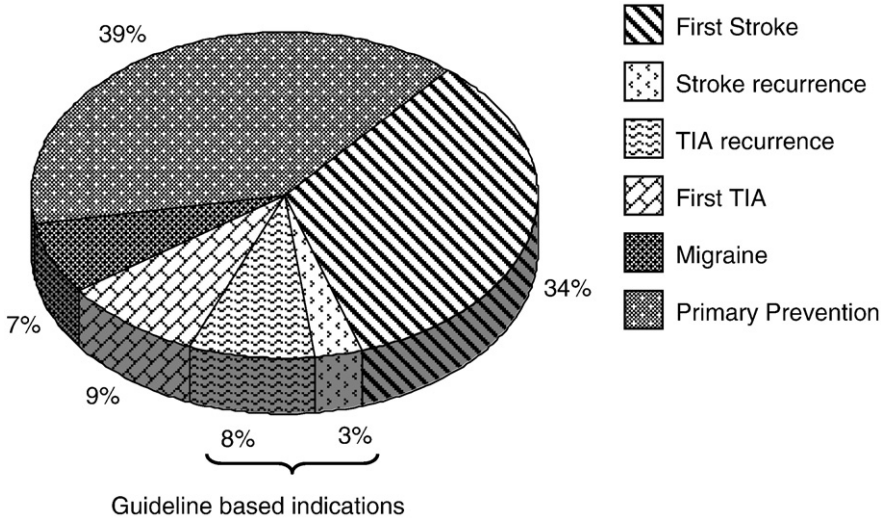

Fig. 1. Indications for PFO closure in 99 pts (group 1). See text for details.

Table 3
Events during follow-up. See text for details.

	All pts $n=446$	Group 1 (closed PFO) $n=99$	Group 2 (unclosed PFO) $n=347$	p
Death	10 (2.2%)	1 (1%)	9 (2.6%)	0.58
TIA	8 (1.8%)	5 (5%)	3 (0.8%)	0.02
Stroke	4 (0.9%)	1 (1%)	3 (0.86%)	0.63
Fatal Stroke	1 (0.2%)	1 (1%)	0	0.50
Non fatal Stroke	3 (0.6%)	0	3 (0.8%)	0.81
Endocarditis	1 (0.22%)	1 (1%)	0	0.50
Peripheral embolism	1 (0.22%)	1 (1%)	0	0.50
Pulmonary embolism	1 (0.22%)	0	1 (0.28%)	0.50
Aspecific neurological symptoms	7 (1.5%)	5 (5%)	2 (0.5%)	0.007

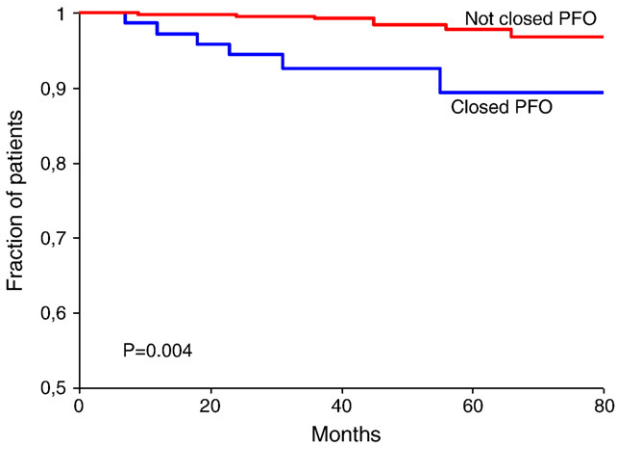

Fig. 2. Kaplan–Meier analysis of survival free from cerebrovascular events during follow-up. See text for details.

relationship between PFO and CS has not been established yet and still remains controversial [6,24]. Initial studies that documented an increased risk of stroke related to the presence of PFO were conducted on pts at increased risk of stroke, either because they had previous stroke [1–4,25] or because of associated abnormalities or morbid conditions, such as ASA and/or large size of PFO-related shunt [26–28], the presence of deep venous thrombosis [29,30], right atrial abnormalities [31] and hypercoagulability [32–35]. On the other hand, data obtained from 2 prospective population-based cohort studies suggested a low risk of *first stroke* among pts with PFO [11,12]. In the Northern Manhattan Study (NOMAS), presence of PFO was not related to an increased stroke risk in a multiethnic cohort of both men and women: stroke incidence was 12.2 per 1000 person-years in subjects with a PFO and 8.9 per 1000 person-years in those without it (difference not significant). Furthermore, the frequency of stroke in the general population was considered low (6.2% during a median follow-up of ~6.5 years, corresponding to annual incidence rate of ~1%) [11]. Again, PFO was not an independent predictor of stroke among subjects older than 45 years of age in the SPARC study: the adjusted PFO-related hazard ratio of cerebrovascular events was 1.46 (95% CI 0.74 to 2.88)[12]. Similar conclusions on the PFO-related stroke risk were drawn by the same investigators using a case–control design [36].

In addition, several studies have consistently found that the presence of a PFO does not increase the risk of *recurrent stroke*. The best data concerning PFO and stroke recurrence come from 3 prospective cohort studies [7–9]. None of these studies found an increased risk of recurrent stroke in pts with a PFO compared with those without PFO, and a pooled analysis of the 3 studies reported a relative risk of 0.95 (95% CI, 0.62 to 1.44) [10].

Of interest, in our study, which included both subjects with and without previous cerebral ischemia, the stroke rate (first event or recurrence) during follow-up was respectively 1% in subjects with closed PFO and 0.8% in those with unclosed PFO (difference not significant), with a stroke risk comparable to the one estimated in the general population (≈1% per year) [37,38].

An important issue that should be emphasized is the large eterogeneity observed in this study in the decision to close the PFO (illustrated in Fig. 1), reflecting the different opinions of physicians caring for pts and their adherence to current guidelines: most pts (89%) underwent PFO closure after the first cerebrovascular event, or for migraine or for primary prevention in occasionally detected PFO, conditions for which there is no published evidence that surgical/percutaneous PFO treatment improves prognosis [39,40]. On the other hand, only 11% of group 1 pts had an accepted indication to PFO closure, that is recurrent stroke or TIA despite medical therapy, as recommended by published guidelines [14,15]. However, despite the nonrandomized design of this study, follow-up of our pts showed few events not only in group 1 pts but also, and specially, in group 2 pts, in whom TIAs were even less common. Furthermore, survival free from cerebrovascular events was significantly better in group 2 compared to group 1 pts (Fig. 2).

These data support the need for prospective randomized studies comparing the effects of conventional medical therapy and PFO closure on prognosis in selected group of pts with "symptomatic" PFO [13,41].

Another point of interest is represented from the presence, in more than half of our pts with cerebrovascular events (7 out of 12, 58%) during follow-up, of other clinical and echocardiographic features potentially responsible for cardioembolism, such as atrial fibrillation, mitral valve disease, thoracic aortic atherosclerosis, in alternative to PFO, confirming previous studies [42–45]. Prompt detection of these

Table 4
Characteristics of patients with cerebrovascular events during follow-up.

	Pt	Age/sex	Initial clinical presentation	ASA	Atrial fib.	Mitral valve disease	Thoracic aorta atherosclerosis	Event during follow-up
Group 1	M.C.	54/M	Stroke	No	No	No	No	TIA
	T.M.	43/F	Stroke	No	No	No	No	TIA
	N.G	30/M	TIA	No	No	No	No	TIA
	C.M.	70/F	Stroke	Yes	No	Yes	Yes	TIA
	N.E.	33/M	TIA	No	No	No	No	TIA
	P.F.	59/M	Occasional	Yes	No	Yes	No	Stroke
Group 2	F.L.	33/M	TIA	Yes	No	No	No	TIA
	L.M.	76/F	Stroke	No	No	No	Yes	Stroke
	C.A.	76/F	Occasional	No	Yes	No	No	Stroke
	S.V.	58/F	Stroke	No	No	No	Yes	TIA
	G.M	75/M	Occasional	No	No	No	Yes	TIA
	D.B	80/M	Occasional	Yes	Yes	Yes	Yes	Stroke

abnormalities is relevant both for understanding the "failure" of PFO treatment in preventing new cerebrovascular events and for selecting the appropriate therapeutic option.

5. Study limitations

First of all, the cohort evaluated in this study was heterogeneous as far as neurological diseases. There were some patients with stroke, some with TIA, others with migraine and some with no neurological disease, but with various cardiac diseases. However, these patients represent a general population consecutively referred to Echo Lab and resulted to be affected by PFO.

We do recognize that the inclusion of TIA as an endpoint may be misleading, since it is difficult to be evaluated – even by the neurologist – especially by an annual phone call survey.

Furthermore, this study had a prospective non randomized design, with pts consecutively enrolled following recognition of PFO during echocardiographic examination performed for different clinical indications. Pts included were different for clinical presentation and therapeutic choices (closure or medical treatment), the latter left to experience and preferences of personal physicians and not reflecting an evidence-based approach, as opposed to a randomized trial.

Most patients were on treatment with antiplatelet drugs or vitamin K antagonists, according to physicians decisions and not a per protocol approach. Due to the small number of pts with prothrombotic defect or conditions, we could not assess the clinical relevance of their association with PFO. However, the role of thrombophilia in pathogenesis of ischemic stroke is still controversial [46].

Therefore, the results of the follow-up may be biased, if compared to the results of randomized studies. However, to date no randomized clinical trials comparing the effects of conventional medical therapy and PFO closure have been completed and published.

Hence, our data provide, in our opinion, relevant insights on treatment and outcomes of PFO subjects from the "real world", while waiting for the results of ongoing studies.

6. Conclusions

Our study suggests that new cerebrovascular events are rare in *unselected subjects* with PFO, even in those with previous cerebral ischemia and in those who have not undergone PFO closure, with an event rate very similar to the one observed in general population. These data confirm recent evidence from other observational studies, which lead to reconsider the need for PFO closure. Considering the relevant therapeutic implications, these data require confirmation in ongoing, prospective, randomized clinical trials.

6.1. Addendum

Preliminary results of the CLOSURE I trial have been recently released. The trial failed to achieve its primary endpoint and PFO closure, using the Starflex device, was not superior to the best medical therapy for preventing recurrent stroke or TIA [47].

Disclosures

There are no conflicts of interest to disclose.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [48].

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