Long-term effectiveness of early administration of glycoprotein IIb/IIIa agents to real-world patients undergoing primary percutaneous interventions: results of a registry study in an ST-elevation myocardial infarction network

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Aims To evaluate the clinical impact of early administration of glycoprotein IIb/IIIa agents (IIb/IIIa agents) in the context of a dedicated hub and spoke network allowing very prompt pharmacological/mechanical interventions.

Methods and results Using a prospective database, we conducted a cohort study of ST-elevation myocardial infarction (STEMI) patients (n = 1124) undergoing primary percutaneous coronary interventions (PPCIs) and IIb/IIIa agents administration (period, 2003–2006). Comparisons were planned between patients receiving early IIb/IIIa agents administration (in hub/spoke centre emergency departments or during ambulance transfer; early group, n = 380) or delayed administration (in the catheterization laboratory; late group, n = 744). The primary outcome measure was long-term overall mortality/re-infarction. Baseline characteristics of the two groups were largely comparable. Angiographically, early group patients more often achieved pre-PPCI TIMI Grade 2–3 and TIMI Grade 3 flow. Clinically, the early administration group experienced lower 2-year risk of unadjusted mortality/re-infarction (17 vs. 23%; P = 0.01). After adjustment for potential confounders, early administration was associated with favourable outcome in the overall population (HR = 0.71, P = 0.03) and in high-risk subgroups (TIMI risk index >25, HR = 0.64, P = 0.02; Killip class >1, HR = 0.54, P = 0.01).

Conclusion In patients treated by PPCI within a STEMI network setting, early administration of IIb/IIIa agents may provide long-term clinical benefits. Notably, these results appeared magnified in high-risk patients.

Keywords Myocardial infarction • Percutaneous coronary interventions • Glycoprotein IIb/IIIa inhibitors

Introduction

Primary percutaneous coronary intervention (PPCI) is the preferred approach for re-establishing coronary perfusion in ST-elevation myocardial infarction (STEMI) when delivered in a timely fashion and in centres where appropriate facilities are available. Nevertheless, in many geographical areas, logistic considerations make it difficult to perform PPCI within the recommended 90 min from the first medical contact.7 The thrombus disaggregating effect of glycoprotein IIb/IIIa agents (IIb/IIIa agents) reduces the pre-PPCI thrombus burden, favours earlier culprit vessel reperfusion, and reduces the peri-procedural distal embolization.3–5 Randomized studies6,8 and a meta-analysis9 showed that IIb/IIIa agents therapy can improve the angiographic and clinical
results of PPCI. Other studies showed that pre-treatment with IIb/IIIa agents (for 10–60 min) is associated with an initial TIMI 2–3 flow ranging from 35 to 55%.8–17 Owing to the delays encountered in many real-world settings, early administration of IIb/IIIa agents was proposed. However, the currently published randomized trials that endeavoured to evaluate this strategy showed conflicting angiographic and clinical results.8–21 We conducted a single-centre registry study (set in a hub and spoke STEMI network) to evaluate the effectiveness of a strategy of early administration of IIb/IIIa agents compared with the traditional (delayed) administration strategy.

Methods

Study design and setting

This retrospective cohort study (conceived in accordance with the principles of the most recent revision of the Declaration of Helsinki) was based on the database (at S. Orsola-Malpighi Hospital) of one of the two centralized PCI centres participating in the ‘Bologna STEMI hub and spoke network model’.22–25 Both centralized PCI intervention laboratories in the Province of Bologna (3702 km², 950 000 inhabitants) are available at short notice on a 24 h basis within their hub-and-spoke catchment zones (containing a total of 10 peripheral locations). Since June 2003, STEMI patients who call the ‘118 Emergency Medical Service’ from a location within about 90 min’ drive from an interventional laboratory on diagnosis of high-risk STEMI, although non-high risk patients generally receive thrombolytic treatment. The database used for the equation: 27 [heart rate in b.p.m. /blood pressure in mmHg.28 Major bleeding was defined as the occurrence of intracranial or retroperitoneal bleeding or clinical signs of haemorrhage (including imaging), accompanied by a >5 g/dL drop in haemoglobin. Recurrent myocardial infarction was defined as a new increase in the creatinine kinase MB fraction to less than two times the normal upper limit, accompanied by chest pain and/or ECG changes. In-hospital events were: overall mortality, recurrent myocardial infarction, target vessel revascularization, stroke, and major bleeding. Long-term major cardiovascular events (MACE) were: overall mortality, recurrent myocardial infarction, and target vessel revascularization. Pain-to-balloon time (total ischaemic time) was defined as the interval (in min) between onset of symptoms and first balloon dilatation. Although left ventricular angiography was not performed, all patients received two-dimensional echocardiographic evaluations in the first 24 h after PPCI to assess left and right ventricular ejection fractions and exclude mechanical complications.

Primary percutaneous coronary intervention protocol

Before arriving at the catheterization laboratory, all patients received aspirin (250 mg i.v.) and unfractionated heparin (5000 IU i.v.). The use of β-adrenergic blocking agents and nitrates during the PCI procedure was strongly encouraged. In the first 2 years of the provincial network (2003–2004), early administration of IIb/IIIa agents was mainly encouraged in patients transferred from spoke hospitals and in patients with large myocardial infarction (i.e. anterior myocardial infarction). Furthermore, until 2005, the lack of ambulance refrigeration facilities precluded administration of IIb/IIIa agents during pre-hospital triage. Since 2005, early administration has been more strongly encouraged in all settings. Thus, early administration of IIb/IIIa agents became more frequent during the study period: 24% (37/240) in 2003, 28% (85/302) in 2004, 41% (118/286) in 2005, and 41% (120/296) in 2006. The drugs administered were Abciximab [0.25 mg/kg as an intravenous bolus, followed by 0.125 µg/kg/min for 12 h (n = 966)] and Tirofiban [as a 10 µg/kg (n = 66) or 25 µg/kg (n = 92) intravenous bolus, always followed by 0.15 µg/kg/min for 18–24 h]. After PPCI, if a stent was deployed, patients were given a loading dose of 300 mg clopidogrel as soon as possible followed by a maintenance dose of 75 mg for at least 1 month (6–12 months for drug eluting stents).

Angiographic analysis and definitions

Quantitative coronary angiography was analysed by experienced site investigators blind to all data apart from the coronary angiogram. Culprit vessel TIMI flow grades were assessed before and after PPCI. Stratification of patients into ‘low risk’ and ‘non-low risk’ subsets was based on the presence of at least one of the main risk profile criteria proposed by TIMI investigators (age ≥70 years, anterior STEMI, heart rate ≥100 b.p.m. on admission).26 TIMI risk index was calculated using the equation:27 [heart rate in b.p.m. x (age in years/10)]²/systolic blood pressure in mmHg. Cardiogenic shock (secondary to left or right ventricular dysfunction) was defined as a persistent systolic blood pressure <90 mmHg (recorded in the catheterization laboratory before PPCI or aortic balloon pump implantation), unresponsive to i.v. fluid administration, or requiring vasopressor agents to maintain systolic pressure ≥90 mmHg.28 Major bleeding was defined as the occurrence of intracranial or retroperitoneal bleeding or clinical signs of haemorrhage (including imaging), accompanied by a >5 g/dL drop in haemoglobin. Recurrent myocardial infarction was defined as a new increase in the creatinine kinase MB fraction to less than two times the normal upper limit, accompanied by chest pain and/or ECG changes. In-hospital events were: overall mortality, recurrent myocardial infarction, target vessel revascularization, stroke, and major bleeding. Long-term major cardiovascular events (MACE) were: overall mortality, recurrent myocardial infarction, and target vessel revascularization. Pain-to-balloon time (total ischaemic time) was defined as the interval (in min) between onset of symptoms and first balloon dilatation. Although left ventricular angiography was not performed, all patients received two-dimensional echocardiographic evaluations in the first 24 h after PPCI to assess left and right ventricular ejection fractions and exclude mechanical complications.

Outcome measures

Comparisons were made between those patients who received early IIb/IIIa agents administration in hub/spoke centre emergency departments or during ambulance transfer (‘early administration group’) and patients submitted to the traditional delayed strategy of IIb/IIIa agents administration directly in the catheterization laboratory (‘late administration group’). The main clinical outcome measure was long-term freedom from death/re-infarction. A decision to perform subgroup analysis of patients with Killip class >1 and with TIMI risk index >25 (corresponding to the median value of the study population) was taken before the analysis.
Ascertainment of events
For all patients, follow-up was closed on 30 September 2007. In-hospital outcome data were obtained from the main database, and by telephoning the peripheral hospitals to which patients had been transferred (as systematically recorded on the database). Long-term outcomes were ascertained by the Emilia-Romagna Regional Health Agency from codified Hospital Discharge Records (obligatorily archived for all public/private Italian hospitals) and Municipal Civil Registries. Hospital records were reviewed for additional information whenever deemed necessary.

Statistical analysis
Continuous data were expressed as mean ± SD or median (25th–75th percentiles), as appropriate, and categorical data as counts (percentages). Group comparisons of categorical variables were conducted using the χ² test with Yates correction. The two-tailed Student’s t-test was used to compare normally distributed continuous variables. Comparisons of non-normally distributed variables were conducted using the Mann–Whitney rank sum test. Estimated long-term outcome measures of the early and late IIb/IIIa agents administration groups were assessed by the Kaplan–Meier method and compared using the log-rank test. Cox proportional-hazard regression analysis was used to assess whether early IIb/IIIa agents administration was an independent predictor of long-term death/re-infarction (primary outcome measure) in the overall study population and in the pre-specified patients sub-groups (TIMI risk index >25 and Killip class >1). The models were created avoiding model building procedures and choosing 14 clinically relevant variables as: age

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patients’ clinical characteristics and treatment delays (determined at catheterization laboratory arrival)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Early Group (n = 380)</td>
</tr>
<tr>
<td>66 ± 13</td>
<td>67 ± 13</td>
</tr>
<tr>
<td>Men [n (%)]</td>
<td>289 (76)</td>
</tr>
<tr>
<td>History of smoking [n (%)]</td>
<td>253 (67)</td>
</tr>
<tr>
<td>Hypercholesterolemia [n (%)]</td>
<td>176 (46)</td>
</tr>
<tr>
<td>Diabetes [n (%)]</td>
<td>67 (18)</td>
</tr>
<tr>
<td>Insulin-dependent diabetes [n (%)]</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Hypertension [n (%)]</td>
<td>219 (58)</td>
</tr>
<tr>
<td>Family history of CVA [n (%)]</td>
<td>131 (35)</td>
</tr>
<tr>
<td>Prior myocardial infarction [n (%)]</td>
<td>47 (12)</td>
</tr>
<tr>
<td>Prior CABG [n (%)]</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Prior PCI [n (%)]</td>
<td>23 (6)</td>
</tr>
<tr>
<td>Anterior myocardial infarction [n (%)]</td>
<td>218 (57)</td>
</tr>
<tr>
<td>Heart rate (b.p.m.)</td>
<td>75 ± 20</td>
</tr>
<tr>
<td>Systolic pressure (mmHg)</td>
<td>128 ± 30</td>
</tr>
<tr>
<td>Killip class &gt;1 [n (%)]</td>
<td>80 (21)</td>
</tr>
<tr>
<td>Non-low risk patient [n (%)]</td>
<td>288 (76)</td>
</tr>
<tr>
<td>TIMI risk index</td>
<td>24 (16–31)</td>
</tr>
<tr>
<td>Cardiogenic shock [n (%)]</td>
<td>40 (11)</td>
</tr>
<tr>
<td>Post-anoxic coma [n (%)]</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Off-hours PPCI [n (%)]</td>
<td>248 (65)</td>
</tr>
<tr>
<td>Triage groups [n (%)]</td>
<td>Pre-hospital</td>
</tr>
<tr>
<td>PPCLI-hospital</td>
<td>74 (20)</td>
</tr>
<tr>
<td>Spoke hospitals</td>
<td>187 (49)</td>
</tr>
<tr>
<td>Time delays (min)</td>
<td>Pain-to-ECG</td>
</tr>
<tr>
<td>ECG-to-laboratory</td>
<td>60 (42–84)</td>
</tr>
<tr>
<td>Laboratory-to-balloon</td>
<td>24 (15–30)</td>
</tr>
<tr>
<td>Pain-to-balloon time</td>
<td>197 (130–314)</td>
</tr>
<tr>
<td>ECG-to-balloon time</td>
<td>82 (63–107)</td>
</tr>
<tr>
<td>Pain-to-balloon time ≤ 180 min [n (%)]</td>
<td>164 (43)</td>
</tr>
<tr>
<td>ECG-to-balloon time &lt; 90 min [n (%)]</td>
<td>228 (60)</td>
</tr>
<tr>
<td>Pain-to-IIb/IIIa agents</td>
<td>126 (75–235)</td>
</tr>
<tr>
<td>IIb/IIIa agents-to-balloon</td>
<td>65 (48–84)</td>
</tr>
</tbody>
</table>

Continuous data are expressed as means ± SD or as medians (25th–75th percentiles).
CVA, cardiovascular accident; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention; ECG, electrocardiogram.
Results

Study population

During the study period, 1357 patients underwent PPCI at our institution within 12 h of symptoms without thrombolysis pre-treatment: of these, 1124 (83%) were treated with IIb/IIIa agents and were included in the present analysis. Early IIb/IIIa agents administration was performed in 380 (34%) patients (‘early administration group’), whereas the remaining 744 patients received IIb/IIIa agents in the catheterization laboratory immediately before PPCI (‘late administration group’). Table 1 summarizes patients’ clinical characteristics and risk factors according to the two treatment groups. In both groups of patients, pre-hospital triage accounted for ~30% of referrals (referral from spoke hospitals was more common in the early administration group, and PPCI–centre referral was more frequent in the late administration group). In line with these referral route distribution differences, the early administration group had somewhat longer ECG-to-balloon and ECG-to-balloon time. Median pain-to-balloon time was ~3 h in both groups (13 min longer in the early administration group). Regarding drug exposure time, the interval between IIb/IIIa agents administration and PPCI was on average 58 min longer in the early administration group; at PPCI, patients in the early administration group had a slightly lower mean heart rate, higher mean systolic pressure, and consequently a lower median TIMI risk index value (Table 1). Table 2 summarizes patients’ angiographic and procedural characteristics in the two treatment groups.

In-hospital findings

Pre-PPCI vessel patency was more frequent in the early administration group in terms of both TIMI Grade 3 flow (64/380, 17% vs. 93% of both the early (338/364) and late (643/691) IIb/IIIa agents administration groups (P = 0.99), statins in 57% of both the early (210/364) and late (394/691) IIb/IIIa agents administration groups (P = 0.96), and angiotensin-converting enzyme-inhibitors in respectively the 84% (306/364) and 82% (586/691) of the early and late IIb/IIIa agents administration groups (P = 0.50).

Long-term outcome

Outcomes were ascertained for 1121 (99.7%) patients. Figure 2 reports Kaplan–Meier curves in the overall study population according to IIb/IIIa treatment strategy. During a median follow-up of 20 months (25th–75th percentile, 13–32), the early administration group showed lower estimated 2 year rates of all-cause mortality/re-infarction (17 vs. 23%; P = 0.01), all-cause mortality (11 vs. 15%; P = 0.02), and MACE (23 vs. 30%; P = 0.01). Differences were more apparent in the high-risk subgroups. Among patients with TIMI risk index >25 (n = 587), those who received
early administration \((n = 175)\) showed remarkably lower 2 year rates of death/re-infarction (23 vs. 33\%; \(P = 0.02\)), overall mortality (16 vs. 25\%; \(P = 0.02\)), and MACE (30 vs. 39\%; \(P = 0.04\)) (Figure 3). Among patients with Killip class >1 \((n = 265)\), the 2 year rates were 26 vs. 49\% \((P = 0.001)\) for mortality/re-infarction; 21\% vs. 39\% \((P = 0.006)\) for overall mortality; 30\% vs. 54\% \((P = 0.001)\) for MACE (Figure 4). At Cox multivariable regression analysis [adjusting for potential clinical, logistic, and procedural confounders (see above)], early administration of \(\text{IIb/IIIa} \) agents was associated with a significant reduction of death/re-infarction in the overall population \((HR = 0.71; 95\% CI 0.53–0.96; \ P = 0.03)\). Significant reductions in death/re-infarction were recorded in both high-risk sub-groups: TIMI risk index >25 \((HR = 0.64; 95\% CI 0.44–0.92; \ P = 0.02)\); Killip class >1 \((HR = 0.54; 95\% CI 0.33–0.88; \ P = 0.01)\).

**Discussion**

This study, set in a highly organized hub and spoke STEMI network, regards unselected (and therefore mainly high risk) patients who underwent rapid \(\text{IIb/IIIa} \) agents administration and PPCI (coupled with a rather short average reperfusion time). The results suggest that a strategy of very early initiation of \(\text{IIb/IIIa} \) agents may indeed confer long-term clinical benefits in high-risk patients without any excess risk of major bleeding in hospital. The thrombus disaggregating effects of \(\text{IIb/IIIa} \) agents can reduce the
Figure 2. Kaplan–Meier curves for overall study population (n = 1124) according to primary percutaneous coronary intervention IIb/IIIa facilitation strategy: (A) overall mortality, (B) mortality/re-infarction, and (C) major cardiovascular events.
pre-PPCI thrombus burden, favouring earlier culprit vessel reperfusion\(^\text{3–5}\) and, in line with previously reported studies,\(^\text{8–19}\) early administration of IIb/IIla agents in our data was associated with higher proportions of patients achieving initial TIMI Grade 2–3 flow. Observational studies indicate that spontaneous initial TIMI 3 flow is associated with improved myocardial salvage.

**Figure 3** Kaplan–Meier curves for TIMI risk index >25 sub-group (n=587) according to primary percutaneous coronary intervention IIb/IIla facilitation strategy: (A) overall mortality, (B) mortality/re-infarction, and (C) major cardiovascular events.
and survival in STEMI patients. Early administration of IIb/IIIa agents is an attractive concept, the potential of which remains to be fully explored, at least in high-risk patients. A subgroup analysis of the ADMIRAL trial first suggested that abciximab might exert greater clinical efficacy when administered before arrival in the catheterization laboratory. Several small randomized studies showed...

**Figure 4** Kaplan–Meier curves for Killip class $>1$ sub-group ($n = 265$) according to primary percutaneous coronary intervention IIb/IIIa facilitation strategy: (A) overall mortality, (B) mortality/re-infarction, and (C) major cardiovascular events.
of mainly non-high-risk patients showed that early IIb/IIIa agents administration can improve important surrogate endpoints. However, these studies were underpowered to test the clinical efficacy of the pharmacological improvements in vessel patency. Notably pooled analyses of randomized trials\textsuperscript{22--25} showed conflicting results and the recently concluded FINESSE trial\textsuperscript{22} failed to detect clinical benefits from IIb/IIIa agents facilitation therapy.

In our peculiar hub and spoke STEMI network setting, early administration of IIb/IIIa agents was associated with a substantial (26\%) crude reduction in the long-term risk of death/re-infarction (accompanied by sizable reductions in long-term mortality and MACE) which also reached significance at Cox proportional hazards analysis. Remarkably, the favourable associations appeared more pronounced in high-risk subgroups (TIMI risk index >25, Killip class >1). These findings should be interpreted in the context of a high-risk population submitted to timely treatment in terms of both pharmacological administration and mechanical revascularization. The observation that outcome benefits appeared to occur more frequently in patients at higher risk may not be altogether surprising in the light of studies of conventional (i.e. non-early) IIb/IIIa agents administration: the only controlled trial where survival benefits were recorded allowed enrolment of high-risk STEMI patients;\textsuperscript{26} furthermore, some evidence of clinical benefit also emerged in a non-randomized study focusing on patients with cardiogenic shock.\textsuperscript{27} Notably, the American College of Cardiology/American Heart Association guidelines state that a strategy of facilitated PCI ‘holds promise’ (as a class IIa indication) in higher risk patients when PCI is not immediately available.\textsuperscript{28} In our STEMI network (inaugurated in 2003), implementation of standardized protocols allows fast inter-hospital transfers and—in the case of telemedicine-guided pre-hospital triage—emergency department bypass.\textsuperscript{29--31} In a significant number of our facilitated patients, IIb/IIIa agents administration and mechanical revascularization were completed in the early phase of ischaemia (within 3 h from the onset of pain): in other words, within the so-called ‘golden window’ when the clot is less resistant and myocardial salvage—and therefore the potential for clinical benefit—may be substantial.\textsuperscript{32} It is conceivable that the apparent discrepancy with the disappointing results of the FINESSE trial\textsuperscript{22} may be attributable to the different clinical and logistic characteristics of the two study populations [in our patients a more severe clinical picture, shorter times from pain-to-IIb/IIIa facilitation (126 vs. 165 min), from IIb/IIIa facilitation-to-revascularization (65 vs. 90 min), and from pain-to-revascularization (197 vs. 255 min)]. Finally, our findings are in line with the recently published On-TIME 2 trial that showed improvements in ST-segment resolution and 30 day clinical outcome in STEMI patients treated with very rapid pre-hospital administration of tirofiban\textsuperscript{21} and with the yet unpublished results (Dudek D, oral presentation, ESC 2007) of the EUROTRANSFER multicentre, prospective, registry (1086 patients) (ClinicalTrials.gov Identifier: NCT00378391) that showed favourable in-hospital and 30 day clinical outcomes in transferred STEMI patients treated with early administration of abciximab and PCI. Although vulnerable to hidden confounding factors and other sources of bias, this large single-centre registry study may help fill out the picture gained from the available randomized studies, suggesting relevant hypotheses for future studies. The characteristics of the two treatment groups were generally fairly well balanced. However, at admission to the catheterization laboratory, the early treatment group showed slight but significant differences in systolic pressure and heart rate, indicative of more stable haemodynamic state. Although these differences could largely be attributed to the benefits of early administration in severely affected patients, we cannot exclude that selection bias may also have played a role. The decision to administer IIb/IIIa agents early was left to the medical team performing the triage, and the treatment was more strongly encouraged for patients admitted through spoke hospitals and in the presence of anterior STEMI. Since observational studies are inherently vulnerable to selection bias and unidentified confounding, our results should be interpreted with some caution. This study focused on patients not receiving fibrinolytic therapy living (in the vast majority of cases) within 90 min drive of a PCI centre. Since transfer patients commonly undergo transport times in the 120 min range,\textsuperscript{40} it should be pointed out that the encouraging results of the present study may not be replicated in less favourable settings in which ambulance services are suboptimal or in regions in which transfer distances are unusually long. We think that small but adequately powered randomized studies focusing on high-risk patients in the state-of-the-art ‘rapid transfer’ networks where IIb/IIIa agents can be administered very promptly may be justified to test the hypothesis that facilitation is clinically beneficial in such favourable settings.

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References


Sub-mitral aneurysm

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A 55-year-old Caucasian man presented with a rapid atrial fibrillation which was controlled by Digoxin with spontaneously converting to sinus rhythm. He had history of diabetes. Physical examination showed an infected wound at one toe of the right foot.

There was no electrolyte abnormality, and cardiac-specific enzymes were normal. Conventional echocardiography revealed a mild mitral regurgitation and a suspected cavity in the left atria. Transoesophageal echocardiography and magnetic resonance imaging revealed a large cavity (5 cm of diameter) attached to the atrial side of the posterior leaflet of the mitral valve (Panels A–C), communicating with the ventricle via a single neck. Doppler colour imaging demonstrated blood flow entering the cavity from the left ventricle in systole and returning from the cavity to the ventricle in diastole (Panels D and E). Our first hypothesis was a mitral endocarditis with abscess, but the patient remained asymptomatic with no clinical criteria for infective endocarditis and no septic peripheral emboli. All the cultures were negative.

Coronary angiography showed normal coronary arteries.

The diagnosis of sub-mitral aneurysm was made, and the patient was referred to surgery. The aneurysm was resected (Panel F) and the orifice was repaired with a Dacron® patch. The post-operative course was uneventful. The pathological examination does not suggest an inflammatory aetiology.

Sub-mitral aneurysm is a relatively unknown cardiac pathology, described predominantly in black Africans. They occur in constant anatomic positions, under the posterior leaflet of the mitral valve. It should be differentiated from left ventricular false aneurysm, caused by myocardial necrosis. Atrial fibrillation has not been previously reported in association with sub-mitral aneurysm.

Panel A: Magnetic resonance imaging of sub-mitral aneurysm (red arrow).
Panel B: Multiplane transoesophageal echocardiography. Sub-mitral aneurysm (red arrow). LA indicates left atrium and LV indicates left ventricle.
Panel C: Magnetic resonance imaging of sub-mitral aneurysm (red arrow).
Panel D: Multiplane transoesophageal echocardiography; colour Doppler flow from left ventricle to the sub-mitral aneurysm (green arrow).
Panel E: Magnetic resonance imaging: sub-mitral aneurysm enhancement after contrast injection.
Panel F: Surgical view of the sub-mitral aneurysm. Arrow indicates the single aneurysm neck.

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