New antithrombotic agents: are they needed and what can they offer to patients with a non-ST-elevation acute coronary syndrome?

Frans Van de Werf*

Department of Cardiology, University Hospitals Leuven, Herestraat 49, B-3000 Leuven, Belgium

Introduction

Non-ST-segment elevation acute coronary syndromes (NSTE ACSs), which comprise unstable angina and NSTE myocardial infarction (NSTEMI), are a major public health problem. The primary pathophysiological mechanism responsible for clinical manifestations of NSTE ACS involves the formation of platelet-rich thrombi that develop in response to vascular injury (atherosclerotic plaque rupture or erosion of endothelial monolayer). Current management of NSTE ACS consists of acute administration of antiplatelet and anticoagulant agents, revascularization procedures (in many patients), and long-term treatment with antiplatelet agents as well as statins and agents inhibiting the angiotensin pathways. Despite the frequent use of medical therapy and revascularization procedures, the residual acute and long-term morbidity and mortality associated with NSTE ACS remains high. For example, in the PCI–Clopidogrel in Unstable angina to prevent Recurrent Events (PCI-CURE) trial, the incidence of death or myocardial infarction in patients who were treated with a stent at 1 year was 11.7% in patients given aspirin and 8.7% in patients given aspirin plus clopidogrel. Several factors may play a role in the residual risk for ischaemic events. First, aspirin and P2Y12 ADP receptor antagonists each block only one of the multiple platelet activation pathways leading to thrombotic events, but do not inhibit pathways stimulated by other platelet activators, such as thrombin. Thrombin is the most potent platelet activator, and its stimulatory effect on platelets and thrombosis continues even in the presence of aspirin and an ADP receptor antagonist, thereby potentially leading to acute ischaemic events. Second, variability in individual patient responsiveness to treatment with aspirin or a P2Y12 ADP receptor antagonist is a clinical limitation of current antiplatelet therapy. Third, long-term use of agents that reduce generation and activity of thrombin is not routinely given after the acute event. Fourth, current lipid-lowering therapies do not completely prevent the progression of atherosclerotic lesions or the generation of new lesions. Furthermore, revascularization procedures are effective in restoring or improving myocardial perfusion and improving symptoms, but do not interfere with thrombosis as the underlying pathophysiological mechanism. Finally, registry data indicate that the chronic use of antiplatelets and other proven therapies for secondary prevention after ACS is suboptimal.

* Corresponding author. Tel: +32 16 34 34 72, Fax: +32 16 34 34 67, Email: frans.vandewerf@uz.kuleuven.ac.be

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This article reviews the pathophysiology of NSTE ACS, provides an overview of recommended antithrombotic therapies and current clinical practice, as well as reviews new clinical data on an inhibitor of the platelet PAR-1 thrombin receptor and on new anticoagulants.

**Pathophysiology of non-ST-segment elevation acute coronary syndromes**

Acute presentation of NSTE ACS is precipitated by the rupture of atherosclerotic lesions or erosion of the endothelium, which triggers platelet activation and aggregation, leading to formation of platelet-rich thrombi that impair blood flow and result in ischaemia. Platelet-rich thrombi are stabilized by fibrin mesh which is formed by thrombin-mediated conversion of fibrinogen to fibrin (Figure 1). Thus, the goal of medical therapy is to prevent platelet-mediated thrombosis using antiplatelet agents and inhibit the formation of fibrin mesh with anticoagulants.

Plaque rupture or erosion of the endothelial monolayer exposes blood to the thrombotic subendothelium, leading to the adhesion of circulating platelets and the formation of a platelet monolayer at the site of injury. Adhered platelets are activated by multiple agonists, including thrombin, ADP, and thromboxane A2 (TxA2). Thrombin is the most potent platelet agonist and is active at subnanomolar concentrations. Thrombin activates platelets primarily through the protease-activated receptor 1 (PAR-1), while ADP and TxA2 activate platelets predominantly through the P2Y12 and TPα receptors, respectively (Figure 2). Binding of these agonists to their respective receptors induces changes in platelet function including shape change, secretion of platelet agonists, release of inflammatory mediators, activation of the GP IIb/IIIa receptor, and platelet aggregation. Activated platelets serve as a surface for the assembly and expression of the tenase complex that catalyses the activity of factor X and the prothrombinase complex which converts prothrombin to thrombin (Figure 1). Finally, the fibrin mesh is generated by the conversion of fibrinogen to fibrin.

**Antithrombotic therapies for non-ST-segment elevation acute coronary syndromes**

Based on the pathophysiology of ACS, the primary goal of antithrombotic therapy is to prevent the formation and propagation of platelet-rich thrombi, with inhibition of fibrin-mediated stabilization of platelet-rich thrombi as a secondary goal (Figure 1).

**Antiplatelet therapies**

**Aspirin**

Aspirin irreversibly inhibits cyclooxygenase, which, in platelets, prevents the production of the platelet agonist TxA2, thereby attenuating TxA2-mediated platelet activation. However, because aspirin only blocks the TxA2 pathway, platelet activation and subsequent formation of platelet-rich thrombi/emboli via other pathways may still occur.

**P2Y12 ADP receptor antagonists**

P2Y12 ADP receptor antagonists inhibit ADP-induced platelet activation by irreversibly binding to the platelet P2Y12 ADP receptor. The P2Y12 ADP receptor inhibitors include ticlopidine, clopidogrel, and prasugrel, which are prodrugs that are converted to active metabolite(s), as well as AZD 6140 and cangrelor, which are active drugs that do not require metabolism and are reversible (Table 1). Ticlopidine and clopidogrel are on the market already for many years whereas prasugrel has recently...
been approved by the regulatory authorities in Europe, and AZD6140 and cangrelor are in phase-III development. Similar to aspirin, ADP antagonists are limited by their inability to block platelet activation and subsequent thrombosis in response to agonists other than ADP.

The primary clinical evidence of the benefit of clopidogrel in NSTE ACS are results from the Clopidogrel in Unstable Angina to prevent Recurrent Events (CURE)\(^6\) and PCI-CURE\(^11\) trials. In the CURE trial, a total of 12,562 patients with NSTE ACS received placebo or clopidogrel in addition to aspirin for up to 12 months.\(^6\) Clopidogrel significantly reduced the primary endpoint of death, MI, or stroke (9.3 vs. 11.4%, \(P < 0.001\), Figure 3A).\(^7\) At 30 days after randomization, the rate of the primary outcome was lower in the clopidogrel group vs. placebo (3.9 vs. 4.8%, \(P = 0.007\)). Clopidogrel was associated with an increase in major bleeding complications (3.7 vs. 2.7%, \(P = 0.001\)). Among patients who underwent CABG within 5 days of study drug discontinuation, the rate of bleeding was higher in the clopidogrel group vs. placebo (9.6 vs. 6.3%; \(P = 0.06\)).\(^6\) In PCI CURE, patients undergoing PCI who were pretreated with clopidogrel for a median of 10 days had a significantly lower rate of the primary endpoint of cardiovascular death, MI, or urgent target-vessel revascularization within 30 days of PCI (4.5 vs. 6.4%, \(P = 0.03\)).\(^11\) These results demonstrate that the addition of clopidogrel to aspirin reduces risk of adverse ischaemic outcomes in patients with NSTE ACS. However, the residual morbidity and mortality in patients treated with aspirin plus clopidogrel remains high, and the risk of bleeding is increased compared with aspirin alone.

The TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitorIN with Prasugrel (TRITON) trial\(^4\) included patients with NSTE ACS and ST-segment elevation MI who were scheduled for PCI. Patients were randomized between standard dose of clopidogrel or a loading dose of 60 mg followed by a maintenance dose of prasugrel.\(^24\) Randomized therapy in TRITON was initiated after the coronary anatomy was defined by angiography. The primary endpoint was death from cardiovascular causes, non-fatal MI, or non-fatal stroke at 1 year. The primary efficacy endpoint was in favour of prasugrel when compared with clopidogrel over the 15-month follow-up (9.9 vs. 12.1%, \(P < 0.001\), Figure 3B). The reduction in the primary endpoint was 30% in patients with diabetes vs. 19% in the overall population. A total of 2.4% of patients receiving prasugrel had major bleeding vs. 1.8% of patients who received clopidogrel (\(P = 0.03\)). Significantly more patients treated with prasugrel had fatal TIMI bleeding vs. those treated with clopidogrel (0.4 vs. 0.1%, \(P = 0.002\)). CABG-related TIMI major bleeding was significantly greater with prasugrel vs. clopidogrel (13.4 vs. 3.2%, \(P < 0.001\)). In the 12,844 patients who received at least one coronary stent, prasugrel significantly reduced the primary endpoint (9.0 vs. 11.1%, HR 0.82, \(P = 0.019\)). Stent thrombosis was remarkably reduced with prasugrel: overall 1.13 vs. 2.35%, HR 0.48, \(P < 0.0001\), especially in patients with drug-eluting stents (0.84 vs. 2.341, HR 0.36, \(P < 0.0001\)).\(^25\)

Oral antiplatelet therapy with aspirin (unless contraindicated) and clopidogrel is recommended for all patients presenting with NSTE ACS, with continuation of clopidogrel for 12 months post-discharge, in addition to aspirin.\(^26\)

Table I  Properties of P2Y\(_{12}\) ADP receptor antagonists

<table>
<thead>
<tr>
<th>Agent</th>
<th>Class</th>
<th>Administration</th>
<th>Metabolism</th>
<th>Time to peak platelet inhibition</th>
<th>Reversibility</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticlopidine</td>
<td>Thienopyridine</td>
<td>Oral</td>
<td>CYP450-mediated conversion of pro-drug</td>
<td>4 days(^a)</td>
<td>Irreversible</td>
<td>N/A</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Thienopyridine</td>
<td>Oral</td>
<td>CYP450-mediated conversion of pro-drug</td>
<td>2–6 h(^b)</td>
<td>Irreversible</td>
<td>N/A</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>Thienopyridine</td>
<td>Oral</td>
<td>CYP450-mediated conversion of pro-drug</td>
<td>1 h(^c)</td>
<td>Irreversible</td>
<td>N/A</td>
</tr>
<tr>
<td>Cangrelor</td>
<td>ATP analogue</td>
<td>IV</td>
<td>Not a pro-drug</td>
<td>30 min</td>
<td>Reversible</td>
<td>3–5 min</td>
</tr>
<tr>
<td>Ticagrelor (AZD 6140)</td>
<td>Cyclopentyltriazolopyrimidine</td>
<td>Oral</td>
<td>Not a pro-drug</td>
<td>2 h</td>
<td>Reversible</td>
<td>12 h</td>
</tr>
</tbody>
</table>

\(^a\)With 500 mg dose.

\(^b\)With 600 mg loading dose.

\(^c\)With 60 mg loading dose.

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**Table 1** Properties of P2Y\(_{12}\) ADP receptor antagonists

**Figure 2** Platelet activation pathways stimulated by thromboxane A\(_2\), ADP, and thrombin. The ligands and their receptors are shown. ADP, adenosine diphosphate; TxA\(_2\), thromboxane A\(_2\); PAR, protease-activated receptor.
Glycoprotein IIb/IIIa inhibitors
The aggregation of activated platelets, regardless of the agonist, is mediated by the cross-linking of the GP IIb/IIIa receptor on adjacent platelets by a molecule of fibrinogen, representing the final common pathway to platelet aggregation and formation of platelet-rich thrombi. By preventing the interaction of GP IIb/IIIa receptors with fibrinogen, GP IIb/IIIa inhibitors prevent platelet aggregation (regardless of the agonist) and subsequent thrombus formation. GP IIb/IIIa inhibitors available include eptifibatide, tirofiban, and abciximab. Eptifibatide and tirofiban are competitive inhibitors, whereas abciximab binds permanently to the GP IIb/IIIa receptor.

A meta-analysis of six trials evaluating GP IIb/IIIa inhibition for NSTE ACS in patients treated with aspirin and heparin (a total of 31,402 patients), demonstrated a 9% reduction in the combined rate of death or MI with GP IIb/IIIa inhibitors compared with placebo or control (10.8 vs. 11.8%, \( P = 0.015 \)). The relative treatment benefit was similar in subgroups stratified by risk, resulting in a greater absolute benefit in high-risk patients. Even after a loading dose of 600 mg clopidogrel, abciximab was associated with a significant reduction of the composite death or MI, or urgent target vessel revascularization at 30 days in the Intracoronary Stenting and Antithrombotic Regimen Rapid Early Action for Coronary Treatment 2 (ISAR-REACT 2) trial, which included high-risk patients with NSTE ACS. The rate of major bleeding was higher in patients treated with GP IIb/IIIa inhibitors (24 vs. 1.4%, \( P < 0.0001 \)), but intracranial bleeding rates were similar (0.09 vs. 0.06%, \( P = 0.40 \)). The ESC guidelines recommend GP IIb/IIIa inhibitors as initial, early therapy in high-risk patients only.

Antithrombin therapies
The primary rationale for the use of antithrombin agents is the prevention of thrombin-mediated generation of fibrin, which stabilises the platelet-rich thrombus.

Unfractionated heparin
Historically, unfractionated heparin (UFH) has been the standard antithrombin. Unfractionated heparin is a preparation of heparin molecules that are heterogeneous with respect to molecular weight. The anticoagulant effect of UFH is mediated by binding to circulating antithrombin III, which augments its inhibitory activity towards several coagulation factors, primarily activated thrombin (factor IIa), and activated factor X (factor Xa), a protease that catalyses the generation of thrombin from prothrombin. However, because large heparin molecules exhibit a high degree of non-specific binding to plasma proteins and cells, the anticoagulant activity of UFH is unpredictable and must be monitored. In addition, the binding of UFH to platelet factor 4 on the surface of platelets can result in heparin-induced thrombocytopenia. These limitations have prompted the development of alternative antithrombins, such as low-molecular-weight heparins (LMWHs), anti-Xa agents, and direct thrombin inhibitors (DTIs).

Several relatively small studies have evaluated the efficacy of UFH in patients with unstable angina. A meta-analysis of these studies demonstrated a trend towards more favourable outcomes with aspirin plus UFH vs. aspirin alone, although statistical significance was not achieved.

Low-molecular-weight heparins
Low-molecular-weight heparins are preparations comprised of only heparin molecules of lower molecular weight. These smaller heparin molecules have a relatively low degree of binding to plasma proteins and cells. Low-molecular-weight heparins have a more predictable anticoagulant effect, a longer half-life, and a lower incidence of heparin-induced thrombocytopenia than UFH. Similar to UFH, LMWHs bind and activate antithrombin III, although the relative inhibitory activity of LMWHs towards factor Xa is greater than that of thrombin, resulting in a greater inhibition of thrombin generation.
Several trials have evaluated the efficacy and safety of enoxaparin vs. UFH, but have shown inconsistent results. In two large trials in NSTE ACS patients enoxaparin failed to show superiority over heparin: the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein Ib/IIa Inhibitors (SYNERGY) trial and the A to Z trial. However, a meta-analysis of 12 trials and 49,000 patients with STEMI or NSTE ACS revealed that death or MI by 30 days was significantly reduced with enoxaparin vs. UFH (9.8 vs. 11.4%, OR 0.84, P < 0.001). Major bleeding was higher with enoxaparin (4.3% vs. 3.4%, OR 1.25, P = 0.019). Assessment of the net clinical endpoint of death, MI, or major bleeding at 30 days revealed less frequent events with enoxaparin in the total population of ACS patients (12.5 vs. 13.5%, OR 0.90, P = 0.051). However, there was no significant difference in this endpoint among trials in NSTE ACS.

Indirect factor Xa inhibitors

Indirect factor Xa inhibitors include fondaparinux, a synthetic pentasaccharide that also binds to antithrombin. The pentasaccharide–antithrombin complex is active against factor Xa but not against thrombin, resulting in the inhibition of thrombin generation without the direct inhibition of thrombin activity. The efficacy and safety of the indirect factor Xa inhibitor fondaparinux was evaluated in the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial, in which 20,078 patients with ACS were randomized to receive either fondaparinux or enoxaparin. The rate of primary-outcome events (death, MI, or refractory ischaemia) at 9 days was comparable in the fondaparinux and enoxaparin groups (5.8 vs. 5.7%, respectively) satisfying the non-inferiority criteria. The rate of major bleeding at 9 days was significantly lower with fondaparinux vs. enoxaparin (2.2 vs. 4.1%, P < 0.001). At 30 days, the rate of the primary endpoint was comparable between groups (8.0 vs. 8.6%), while the rate of death was significantly lower with fondaparinux (2.9 vs. 3.5%, P = 0.02).

Direct thrombin inhibitors

Unlike UFH, LMWHs, and indirect factor Xa inhibitors, DTIs, including hirudins, bivalirudin, argatroban, dabigatran (oral agent), and ximelagatran (oral agent), exert their anticoagulant effect by binding directly to thrombin. DTIs do not require monitoring and have not been associated with thrombocytopenia, but have the potential advantage of inhibiting clot-bound thrombin. However, they are not active against factor Xa, and therefore do not block thrombin generation. The efficacy and safety of bivalirudin was evaluated in the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, an open-label study which randomized 13,819 patients with ACS to UFH or enoxaparin plus a GP IIb/IIIa inhibitor, bivalirudin plus a GP IIb/IIIa inhibitor, or bivalirudin alone (with provisional GP IIb/IIIa inhibitor). Bivalirudin alone (with provisional GP IIb/IIIa inhibitor), when compared with heparin plus a GP IIb/IIIa inhibitor, was associated with a non-inferior 30-day rate of the composite ischaemia endpoint of death, MI, or unplanned revascularization for ischaemia (7.8 vs. 7.3%, respectively) and significantly less major bleeding (3.0 vs. 5.7%, P < 0.001). Major bleeding was defined as the cumulative occurrence within 25–35 days after randomization of intracranial or intraocular bleeding, haemorrhage at the access site requiring intervention, haematoma with a diameter of ≥5 cm, a reduction in haemoglobin, reoperation for bleeding, or transfusion. The net clinical outcome endpoint (defined as the occurrence of the composite ischaemia endpoint or major bleeding) was significantly lower with bivalirudin alone (10.1 vs. 11.7%, P = 0.02). There is, however, a concern that in patients pre-treated with clopidogrel, bivalirudin alone may be inferior to the combination of UFH/LMWH plus a GP IIb/IIIa inhibitor.

Although ximelagatran was shown to reduce the incidence of all-cause mortality, non-fatal MI or severe recurrent ischaemia in the ESTEEM trial, this agent has been withdrawn from the market because of liver problems. A similar agent, dabigatran is currently being studied in a phase-II trial of patients with ACS (REDEEM trial).

Direct factor Xa inhibitors

Numerous oral, direct factor Xa inhibitors are in various stages of clinical development, including rivaroxaban, LY517717, YM150, DU-176b, apixaban, and betrixaban, offering the potential of no coagulation monitoring or dose adjustment when compared with current treatment (i.e. vitamin K antagonists). Rivaroxaban and apixaban are oral, direct factor Xa inhibitors in late-stage development for the prevention and treatment of thrombo-embolic disorders. They inhibit clot-associated and free factor Xa activity, and prothrombinase activity, and reduce thrombin generation. Multiple large trials evaluating clinical and safety outcomes with rivaroxaban and apixaban for prevention and treatment of venous thrombosis and in patients with atrial fibrillation have been completed or are about to report the final results. Rivaroxaban was recently approved by the FDA for the prevention of venous thrombosis and pulmonary embolism.

Preliminary data from phase-II studies in patients with NSTE-ACS, APixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial with apixaban and Anti-Xa Therapy to Lower Cardiovascular events in addition to Aspirin with or without thienopyridine therapy in Subjects with Acute Coronary Syndrome (ATLAS) with rivaroxaban suggests a further reduction in ischaemic events at the cost of an increased risk in bleeding. In these studies, the anti-Xa agent was given on top of aspirin alone or on top of aspirin plus clopidogrel for a period of 6 months. More favourable results were seen when these agents were given with aspirin alone. Large phase-III trials have been started in ACS patients.

Intravenous use of antithrombins (UFH, LMWH, fondaparinux, and bivalirudin) is recommended in the acute phase for all patients with NSTE ACS. The choice of agent depends on the risk of both bleeding and ischaemic events, as well as the initial management strategy (early invasive or more conservative management). In patients in whom the initial strategy is conservative, fondaparinux is recommended as the anticoagulant of choice, if an early invasive treatment UFH, bivalirudin, or enoxaparin is preferred.

New insights and opportunities

Collectively, randomized trials and meta-analyses have demonstrated significant reductions in adverse outcomes with aspirin alone and incremental benefits of aspirin plus a P2Y12 ADP
Use of antithrombotic treatments in daily practice

Registry analyses and surveys have provided insights into current treatment patterns and outcomes in patients with NSTE ACS. These data reveal broad use of interventional procedures and antiplatelet therapies. However, as in the randomized studies CURE and TRITON, morbidity and mortality remains significant. The Global Registry of Acute Coronary Events (GRACE) registry reported frequent use of medical and interventional therapies in patients with NSTE ACS (n = 27,558). Among patients treated in 2005, 96% received aspirin (compared with 93% in patients treated in 1999) and over 70% received an ADP receptor antagonist (compared with 20% in patients treated in 1999); PCI increased in NSTE ACS patients by 18% from 1999 to 2005, while CABG declined by 1.8%. Despite the broad use of antiplatelet therapies and interventions, the residual risk for platelet-mediated thrombotic events in patients with NSTE ACS, both acutely and over the long term, remains substantial. In-hospital and 6-month mortality rates were 2.2 and 3.3%, respectively, in 2005. The in-hospital rates of CHF/pulmonary oedema, MI, cardiogenic shock, and stroke were 6.1, 1.7, 1.8, and 0.6%, respectively. At 6 months, the rates of recurrent MI and stroke were 2.9 and 0.7%, respectively.7

The Euro Heart Survey on Acute Coronary Syndromes II (ACS II),8 although a less rigorous study than the GRACE registry, also reveals patterns of medical and interventional treatment in Europe. The ACS II survey (n = 3063) demonstrated an increased use of antiplatelet therapy at discharge in patients with NSTE ACS in 2004 compared with the 2000–2001 Euro Heart Survey on Acute Coronary Syndromes I (ACS I) (although not all the ACS-II sites participated in ACS I). The use of aspirin increased from 88.5 to 94.5% of patients, ticlopidine/clopidogrel use increased from 27.6 to 67.4%, and GP Iib/IIa inhibitor use increased from 10 to 20.8%. Revascularization rates also increased, with 37.1% of patients receiving PCI (compared with 25.4% in ACS I) and 7.4% undergoing CABG (compared with 5.4% of patients in ACS I), although these rates varied widely across hospitals. In-hospital mortality decreased from 4.9 to 4% (P = 0.07) and 30-day mortality decreased from 6.2 to 5.1% (P = 0.04).

Conclusions

Substantial residual morbidity and mortality risk remains in patients with NSTE ACS despite the broad use of mechanical interventions and pharmacologic therapy, including long-term therapy with antiplatelet agents. The high residual long-term morbidity and mortality despite dual antiplatelet therapy with aspirin and ADP receptor antagonist can be partly attributed to suboptimal antithrombotic therapy. Improvements in outcomes in NSTE ACS may be achieved with novel therapeutic approaches and greater use of guidelines-recommended therapy. New therapies that target pathways that are not affected by aspirin or P2Y12 ADP receptor antagonists could provide more comprehensive inhibition of platelet activation and contribute to greater inhibition of platelet-mediated thrombosis. Inhibition of the PAR-1 receptor for thrombin is a new approach in the development of novel antiplatelet agents. PAR-1 inhibition, in combination with current dual antiplatelet therapy, could further reduce ischaemic events without significantly increasing bleeding risk. Furthermore, new oral anticoagulants, such as oral DTIs or oral direct anti-factor Xa agents, may be useful additions to the antiplatelet armamentarium. Whether adding any of these new agents to standard treatment will have a future will depend on their ability to show a net clinical benefit in large phase-III trials.

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New antithrombotic agents for patients with NSTE ACS

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A 10-year-old boy was admitted for a sudden exertional syncope. The ECG showed a regular narrow-QRS tachycardia with RP > PR and negative P waves in inferior leads, suggestive of atrial tachycardia (Panel A). The echocardiogram was normal, and the treadmill test provoked high-density monomorphic ventricular extrasystolia. A 24 h Holter documented two bursts of non-sustained monomorphic ventricular tachycardia (NSMVT) and polymorphic ventricular extrasystoles (Panel B). Magnetic resonance imaging did not find ventricular dilatation or tissue infiltration. The disposition of coronary arteries was normal.

An electrophysiological study was then performed. Conduction intervals and QT were normal. No accessory pathways were found and arrhythmias were not induced. Subsequently, we implanted a loop recorder. Two months later, the patient suffered another witnessed syncope, with recovery in 3 min. Presence of pulse was checked by no one and no particular re-animation manoeuvres was done at all. The device revealed two recorded events: first, a burst of NSMVT followed by atrial ectopic beats and degeneration into ventricular fibrillation, which self-terminated after 19.4 s (Panel C); 1 min later, a short polymorphic ventricular tachycardia, followed by a 6 s pause, four blocked P waves with dissociated QRS complexes, and then 29.4 s of asystolia. Stable activity began with narrow-QRS nodal rhythm (Panel D).

As no reversible condition was found, we indicated the implantation of a cardioverter–defibrillator. After 7 months, syncopes have not recurred. Definitive results of genetic tests for long-QT syndrome and ionic channel diseases mutations are being awaited. So far, the possible diagnosis of idiopathic VF cannot be firmly rejected.

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