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# Early anticoagulation in the current management of NSTE-ACS: Evidence, guidelines, practice and perspectives

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ABSTRACT

Anticoagulant therapy during the acute phase of non-ST elevation acute coronary syndromes (NSTE-ACS) is strongly recommended by current international guidelines. Evidence supporting the use of anticoagulant therapy in the early phase of NSTE-ACS however, is based on dated trials mostly performed in the nineties and recent randomised clinical trials (RCTs), performed during the last 15 years, clearly evidence a dichotomy in the investigation of antiplatelet and anticoagulant strategies. Many innovations have since occurred in the diagnosis and management of NSTE-ACS. Since a RCT evaluating the efficacy of anticoagulant therapy versus placebo in a contemporary setting of NSTE-ACS management is lacking, we provide a systematic review of 1) the randomised data for ATT in the early phase of NSTE-ACS; 2) modern international guidelines, and 3) contemporary clinical practice data. The results are analysed and potential treatment and research strategies are proposed.



## 1. Introduction

Ischaemic heart disease is the leading cause of premature death in the world [1], and anticoagulation remains a cornerstone of its management, due to the involvement of clotting factors in its pathogenesis [2,3]. Given the growing incidence of non-ST-elevation acute coronary syndromes (NSTE-ACS) [4,5], and considering that NSTE-ACS are on average older and burdened by more medical comorbidities than other ACS patients [4], collecting data on efficacy, safety and cost-effectiveness of antithrombotic therapy (ATT) in all phases of NSTE-ACS is of utmost importance.

Contemporary international guidelines express a class I, level of evidence (LOE) B recommendation for early anticoagulation before coronary angiography (CA) in NSTE-ACS [6,7]. The randomised clinical trials (RCTs) cited in the text, however, are almost two decades old, antedating both the advent of dual antiplatelet therapy and the access to CA within a short time from diagnosis; even the more recent trials on early anticoagulation were conducted before the advent of third generation P2Y12 inhibitors [8–13]. The present article is a concise systematic review of 1) the randomised data for ATT in the early phase of NSTE-ACS (including also data on early anticoagulation derived from recent RCTs focused on different antiplatelet strategies); 2) modern international guidelines, and 3) contemporary clinical practice data. The results are analysed and potential treatment and research strategies are proposed.

## 2. Methods

In the present review 'early' was defined as the time preceding CA for patients undergoing an invasive strategy or as the first 48 h of hospitalisation for patients undergoing a conservative strategy. For trials comparing anticoagulant therapies against placebo, three meta-analyses were considered [14–16]. A subsequent literature search focused on randomised phase III trials performed in the setting of NSTE-ACS from 2000 to date, enrolling >1000 patients and comparing either antiplatelet strategies on the background of anticoagulation or anticoagulation strategies on the background of dual antiplatelet therapy. Modern international guidelines on NSTE-ACS were the latest published by European and North American cardiac societies [6,7]. A further literature search focused on contemporary clinical practice in the early phase of NSTE-ACS using the following key words: "anticoagulant therapy", "NSTE-ACS", "early phase". Inclusion criteria were registries or trials performed in the setting of NSTE-ACS from 2010 to date, enrolling >1000 patients and providing details on type and timing of antithrombotic therapy in the early phase. The use of bivalirudin or glycoprotein IIb/IIIa inhibitors (GPIs) was not considered, as it mainly refers to intraprocedural management, whereas the present review focuses on early anticoagulation (before CA).

## 3. Results

### 3.1. Evidence for anticoagulant therapy in the early phase of NSTE-ACS (Table 1)

#### 3.1.1. Heparins versus placebo

Two systematic reviews of RCTs [14,15] are referenced in contemporary NSTE-ACS guidelines [6,7]. They report a reduction in the risk of

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[1] These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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0167-5273/

**Table 1**
Early anticoagulant use in recent RCTs investigating ATT in NSTE-ACS.
Recent randomised control trials (RCTs) focused either on antiplatelet or anticoagulant therapy in the context of NSTE-ACS are tabulated and the information regarding anticoagulant drugs and strategy/timing are highlighted. RCTs on antiplatelet agents do not generally report the timing of concomitant anticoagulant therapy. Conversely, RCTs on anticoagulants often do not generally involve an early invasive approach and never include third generation P2Y12 inhibitors. Overall, there is a high use of GPIs and femoral approach; a placebo arm is never included and an increase of ischaemic efficacy is invariably associated with more bleeding.

| RCT (year of publication) | No. | Antiplatelet/anticoagulant agent tested | Controls | Ischaemic outcomes (HR) | Bleeding outcomes (HR) | Concomitant antithrombotic therapy | Patients undergoing CA | Timing of CA |
|---|---|---|---|---|---|---|---|---|
| *Antiplatelet (AP)* | | | | | | | | |
| CURE (2001) | 12,562 | Clopidogrel | Placebo | 0.80[a] | **1.38**[d] | AP: ASA (100%)<br>AC: UFH or LMWH (73%); **timing not specified** | **44%** | **6 days** |
| TRITON TIMI 38 (2007) | 13,608 | Prasugrel | Clopidogrel | 0.81[a] | **1.32**[d] | AP: ASA (99%), GPIs (54%)<br>AC: UFH (66%) or LMWH (9%), bivalirudin (5%); **timing not specified** | 100% | **Not specified** |
| PLATO (2009) | 18,624 | Ticagrelor | Clopidogrel | 0.84[a] | **1.25**[d] | AP: ASA (97%)<br>AC: UFH (56%), LMWH (51%), fondaparinux (2%), bivalirudin (2%); **timing not specified** | 81% | 4 h |
| CURRENT-OASIS 7 (2010) | 25,086 | Clopidogrel double-dose | Clopidogrel standard dose | 0.86[a] | **1.36**[d] | AP: ASA (high-dose or low-dose, 100%), GPIs (41%)<br>AC: UFH (86%), LMWH (50%), fondaparinux (4%), bivalirudin (5%); **timing not specified** | 100% | 3 h |
| TRILOGY ACS (2012) | 7243 | Prasugrel (medically treated) | Clopidogrel (medically treated) | 0.91[a] | **1.31**[d] | AP: ASA (95%)<br>AC: **not specified** | 42% (before randomisation) | – |
| ACCOAST (2013) | 4033 | Prasugrel pretreatment | Prasugrel no pretreatment | 1.02[a] | **2.95**[d] | AP: ASA (98%), GPIs (4%)<br>AC: UFH (65%), LMWH (30%), fondaparinux (4%), bivalirudin (0.7%); **timing not specified** | 100% | 4 h |
| *Anticoagulant (AC)* | | | | | | | | |
| A-to-Z (2004) | 3987 | Enoxaparin | UFH | 0.88[c] | **3.6**[d] | AP: ASA (99%); Tirofiban (99%) | 60% | 43% by 48 h<br>**60% by 108 h** |
| SYNERGY (2004) | 9978 | Enoxaparin | UFH | 0.95[b] | **1.33**[d] | AP: ASA (99%); Clopidogrel/ticlopidine (65%); GPIs (57%) | 92% | 21.6 h |
| OASIS-5 (2006) | 20,078 | Fondaparinux | Enoxaparin | 1.01[c] | 0.52[d] | AP: ASA (99%); Clopidogrel/ticlopidine (65%); GPIs (18%) | 63% | **2.5 days** |

RCT: randomised clinical trial; AP: antiplatelets; AC: anticoagulants; CA: coronary angiography; Revasc: revascularization; ASA: Acetylsalicylic acid; GPIs: GPIIbIIIa inhibitors; LMWH: low molecular weight heparin; UFH: unfractionated heparin; h: hours.
[a] CV death, MI, stroke.
[b] Death or MI at 14 days.
[c] Death, MI, or refractory ischemia.
[d] NonCABG related TIMI major bleeding.

death or myocardial infarction (MI) with aspirin plus heparin compared to aspirin alone in NSTE-ACS patients. These reviews include RCTs performed between 1988 and 1999. The first is a 1996 meta-analysis by Oler et al., including six RCTs and involving 1353 patients [14]. It reports a relative risk (RR) of death or MI for aspirin plus heparin compared to aspirin alone of 0.67 (95% confidence interval [CI] 0.44–1.02). The summary RRs for secondary endpoints were 0.68 (95% CI 0.40–1.17) for recurrent ischaemic pain; 0.82 (95% CI 0.56–1.20) for MI or death 2 to 12 weeks following randomisation; 1.03 (95% CI 0.74–1.43) for revascularization; and 1.99 (95% CI 0.52–7.65) for major bleeding; thus, all of the 95% CIs crossed unity; anticoagulation was added to variable aspirin doses (75–650 mg daily) and the duration of heparin administration was 3–7 days; only 23% of patients eventually underwent PCI. The second review is a 2000 meta-analysis by Eikelboom et al. including eight RCTs involving 2992 patients [15]. The summary odds ratio (OR) for death or MI during short-term treatment (up to 7 days) with unfractionated heparin (UFH) or low molecular weight heparin (LMWH), compared to placebo or untreated control, was 0.53 (95% CI 0.38–0.73; $p = 0.0001$); the authors themselves emphasize the wide CIs of the point estimates of the individual trials, consistent with a more modest real effect. The latest 2014 Cochrane systematic review and meta-analysis [16] pooled results from eight RCTs involving 3118 patients, randomised to either UFH or LMWH versus placebo, in addition to aspirin. Despite rigorous study selection, the evidence assessed in this review was classified as low quality. No significant difference in overall mortality was found (risk ratio (RRa) = 0.84, 95% CI 0.36–1.98; number needed to benefit (NNTB) = 675). The occurrence of MI was reduced by heparin versus placebo (RRa = 0.40, 95% CI 0.25–0.63; NNTB = 33) with a trend towards more major bleeds (RRa = 2.05, 95% CI 0.91–4.60; NNTharm(H) = 205). The summary risk ratio (RR) for death or MI over all time periods in patients treated with UFH or LMWH, compared with placebo or untreated control was 0.61 (95% CI 0.47–0.80).

### *3.1.2. Early anticoagulant therapy in recent RCTs on ATT in NSTE-ACS (Table 1)*

Modern data on the use of anticoagulant therapy in the early phase of NSTE-ACS could be found both in recent RCTs primarily designed to test anticoagulants and in recent RCTs testing new antiplatelet drugs/strategies. The RCTs published during the last 15 years, comparing either antiplatelet strategies on the background of anticoagulation, or anticoagulation strategies on the background of dual antiplatelet therapy, are listed in Table 1. In all trials there was a high use of GPIs and femoral approach. Moreover, a placebo ("anticoagulant or antiplatelet free") arm was never included.

RCTs focused on antiplatelet agents often involved an early invasive approach [17–23]; they provide scarce information on concomitant

anticoagulant therapy and in most cases it is not possible to deduce the type of anticoagulant given before CA; the use of fondaparinux, even in the most recent trials, appears to be very low (Table 1). Combined and powerful antiplatelet agents, while increasing ischaemic efficacy, were associated with a significantly increased incidence of major bleeds [17,19–23] (Table 1). In parallel, RCTs focused on anticoagulants firstly evaluated the efficacy-safety of LMWH versus UFH [8–12,24] and, subsequently, of fondaparinux versus LMWH [13]. These trials often did not involve an early invasive approach and never included the powerful, third-generation P2Y12 inhibitors (Table 1).

More specifically, SYNERGY [12] found enoxaparin noninferior to UFH (OR 0.96; 95% CI 0.86–1.06) in high-risk patients treated with an early invasive strategy (median time to coronary angiography: 21 h), with a moderate excess of major bleeding as defined by the Thrombolysis In Myocardial Infarction criteria (TIMI; 9.1% vs 7.6%, $p = 0.008$). The most recent and important RCT on anticoagulants in the early phase of NSTE-ACS is the 2006 multicentre OASIS-5 study [13], involving 20,078 patients randomised to receive, upstream, either enoxaparin 1 mg/kg sc bid or fondaparinux 2.5 mg sc od, in addition to standard antiplatelet therapy (only 67% clopidogrel/ticlopidine; 0% ticagrelor/prasugrel). Mean age was 66 years; only 1/2 were diagnosed as having suspected MI at study entry; about 60% underwent CA within the first 8 days after randomisation and only 34% had PCI. The study drug was given for a maximum of 8 days, until discharge or until PCI was performed. Overall, at 9 days, fondaparinux was non-inferior to enoxaparin regarding the primary efficacy outcome measure of death/MI/refractory ischaemia (5.8% vs 5.7%; HR 1.01, 95% CI 0.90–1.13), while TIMI major bleeding at 9 days was significantly lower with fondaparinux (2.2% vs 4.1%; HR 0.52, 95% CI 0.44–0.61; $p < 0.001$). In the 6238 patients undergoing PCI [25], subcutaneous fondaparinux was given on average 12.7 h from the onset of pain for a mean of 2.4 (standard deviation $\pm 1.8$) days before PCI (versus $2.6 \pm 1.8$ days for enoxaparin). In the PCI subgroup, as in the overall trial, fondaparinux was associated at day 9 with a significant reduction in major bleeding (2.4% vs 5.1%; HR 0.46, 95% CI 0.35–0.61; $p = 0.001$) and in the composite endpoint of death/MI/stroke/major bleeding (8.2% vs 10.4%; HR 0.78, 95% CI 0.67–0.93; $p = 0.004$). Vascular access site complications 48 h after PCI, including pseudoaneurysm and large haematoma, were reduced (3.3% vs 8.1%, $p < 0.001$). Radial access was used in only 12% of patients.

### 3.2. International guidelines

The latest guidelines from both the European Society of Cardiology (ESC) [6] and the American Heart Association (AHA)/American College of Cardiology (ACC) [7] strongly encourage early anticoagulation in NSTE-ACS, in addition to dual antiplatelet therapy, at the time of diagnosis, even when the potent P2Y12 inhibitors, prasugrel and ticagrelor, are used (class I, LOE B for ESC, and A or B for AHA/ACC). Fondaparinux is considered as having the most favorable efficacy-safety profile regardless of the management strategy (class I, LOE B). When fondaparinux is not available, enoxaparin or UFH are recommended (class I, LOE B). Pretreatment with a P2Y12 inhibitor (except for prasugrel) is suggested in a recent focused update [26], with a lower class and LOE compared to early anticoagulation (class IIa, LEO C). Importantly, the anticoagulant agent to be used during PCI is dependent on the anticoagulant that has been employed in the early phase. More specifically, in patients already on fondaparinux, UFH is recommended during PCI (class A, LOE B), whereas crossover between UFH and LMWH is strongly discouraged (class III, LOE B). After PCI, discontinuation of anticoagulation "should be considered, unless otherwise indicated" (class IIa, LOE C). Depending on the patient risk, CA in NSTE-ACS should be performed within 2, 24 or 72 h, with the suggested CA timing in the highest-risk group approaching the primary PCI timing of STE-ACS. In medically-treated patients, as no specific recommendation is given, an indication for early anticoagulation can be inferred from ESC Guidelines. Evidence on the optimal duration of anticoagulation in medically managed patients is limited [6,14,15].

### 3.3. Contemporary clinical practice (Fig. 2)

The number of NSTE-ACS patients undergoing CA/PCI has grown over the years, and the interval from diagnosis to CA has steadily decreased [27–31]. Data from registries detailing the use of anticoagulant therapy in the early phase of NSTE-ACS are scarce and tend to overestimate the real use, as no distinction between anticoagulants given prior or during PCI is generally made [28–30,32]. Registries [27,28,31] and RCTs conducted since 2010 [33] providing details about anticoagulant administration and timing are listed in Fig. 2. It should be noted that clinical practice sharply diverges from guidelines regarding early ATT, as pretreatment with dual antiplatelet therapy (DAPT) is preferred over anticoagulation before CA/PCI, and fondaparinux is used less frequently compared to other anticoagulants (Fig. 2), despite a recently documented trend towards increasing use [34]. Patients undergoing medical management represent, in many registries, between 1/4 and 1/3 of the NSTE-ACS population [27,31]. A recent Chinese registry suggests a consistent under-utilisation of anticoagulants [27]. Thus, even in medically managed ACS patients, contemporary real-world data indicate that clinicians limit early anticoagulation [4,35].

## 4. Discussion

### 4.1. Evidence for anticoagulant therapy in the early phase of NSTE-ACS (Fig. 1)

#### 4.1.1. Heparins versus placebo

The meta-analyses of trials evaluating the efficacy and safety of heparins versus placebo present several methodological flaws [14–16]: 1) large 95% CI for many of the trials included; 2) small numbers of patients enrolled in each trial; 3) unclear or high risk of bias for most included studies. In the Cochrane meta-analysis, it is clear how the ischaemic end point is mainly driven by a reduction of MI while patients treated with heparins had a similar risk of death, revascularization, recurrent angina, and thrombocytopenia but higher incidence of major and minor bleeding, compared to placebo. Overall, trials testing early administration of heparins versus placebo in NSTE-ACS are dated, present several biases and report a benefit in terms of reduction of MI but not a clear efficacy in terms of reduction of death, revascularization or recurrent angina. A significant increase in bleeding is always evidenced. Moreover, those trials do not take into account the major innovations have been introduced in the last decade in the contemporary management of NSTE-ACS, including: 1) use of powerful P2Y12 inhibition [17–22,27,29–31]; 2) high rates of invasive management [28,29]; 3) shift from transfemoral to transradial procedures [6,36]; 4) short time from diagnosis to CA [28,29]; 5) almost complete substitution of bare metal stents (BMS) with new-generation drug eluting stents (DES) [37]; 6) changes in the definition of NSTE-ACS due to the adoption of high-sensitivity troponins [38].

#### 4.1.2. Early anticoagulant therapy in recent RCTs on ATT in NSTE-ACS (Table 1, Fig. 1)

We tabulated information from RCTs on ATT, focused both on anticoagulants and on antiplatelet drugs in Table 1, in the effort to highlight the differences between early data and more recent trials. Overall, it is evident that no specific attention was devoted to systematically define anticoagulation protocols in trials of newest antiplatelet drugs, and that even relatively modern trials on an early anticoagulation are of little applicability in a contemporary setting.

Even the SYNERGY trial [12], the only RCT evaluating UFH/LMWH on top of DAPT in patients rapidly undergoing CA, shows many dissonances with contemporary practice, such as lack of powerful P2Y12 inhibition of high-sensitivity troponin for MI diagnosis, low use of DAPT (65%) and radial approach, and high use of GPIs (57%). The OASIS-5 trial [13] shows limitations similar to those of SYNERGY, with a particularly delayed timing of CA (2.5 days in the PCI subgroup [25]). Of note, the bleeding

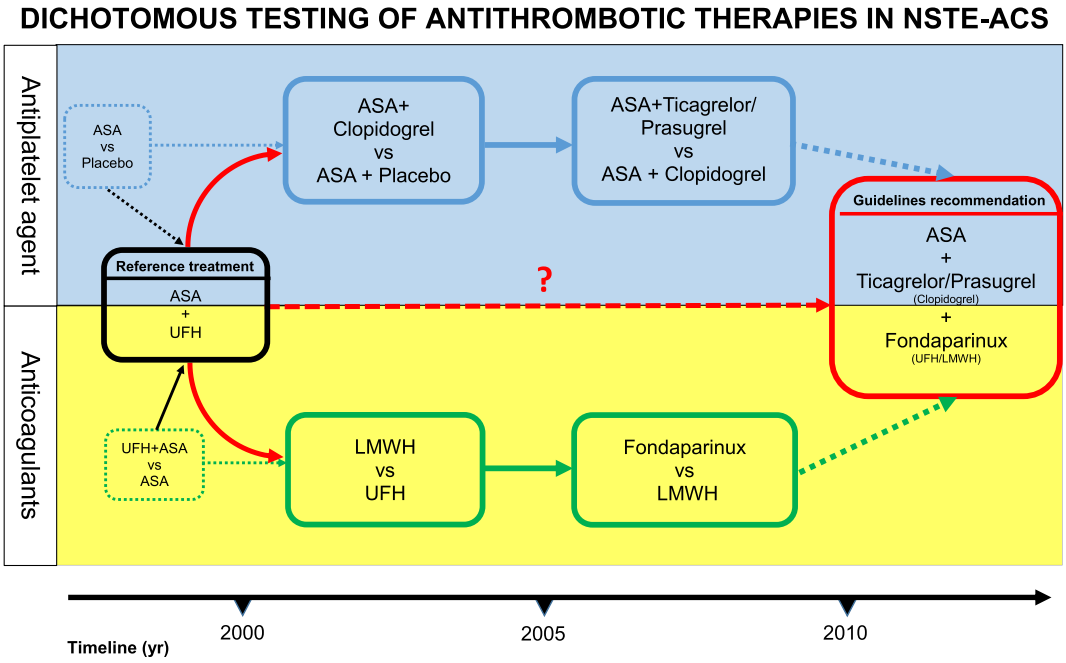


**Fig. 1.** Dichotomous testing of antithrombotic therapies (ATT) in the early phase of NSTE-ACS. Black: meta-analyses cited in guidelines, collected in the nineties, support the use of unfractionated heparin (UFH) in addition to a single antiplatelet agent, typically aspirin (ASA), over single antiplatelet therapy [52]. Blue: meta-analyses of randomised clinical trials (RCTs) demonstrate substantial reduction in death/myocardial infarction (MI) with aspirin vs placebo [53]. Over the next 15 years, further RCTs demonstrate a reduction in ischaemic events, initially by dual vs single antiplatelet therapy and then by more vs less potent dual antiplatelet therapy [17–23]. Green: meta-analyses of RCTs support improved efficacy by replacing UFH by low molecular weight heparin (LMWH) [9,11,12,24] and improved safety by replacing LMWH with fondaparinux [13]. Red: current guidelines recommend triple ATT, combining dual antiplatelet therapy with an anticoagulant agent, although no RCT has compared the efficacy and safety of an early triple versus an early dual antithrombotic regimen [6,7].

reduction seen with fondaparinux in NSTE-ACS was not confirmed in the primary PCI arm (around 4000 patients) of the OASIS-6 study, which enrolled STE-ACS [39]. A trend towards more severe haemorrhage at 9 days (HR 2.18, 95% CI 0.83–5.74), and a large increase in guiding catheter thrombosis (22% vs 0%, $p < 0.001$), as compared to heparin or placebo, form basis for the strong contraindication (class III, LOE B) for fondaparinux before or during PCI in STE-ACS patients in ESC guidelines [40].

In conclusion, little indirect information concerning the efficacy/safety of anticoagulant therapy in the early phase of NSTE-ACS can be found in recent RCTs on ATT since none were conducted in a modern setting, no placebo arm was included, and a precise definition of

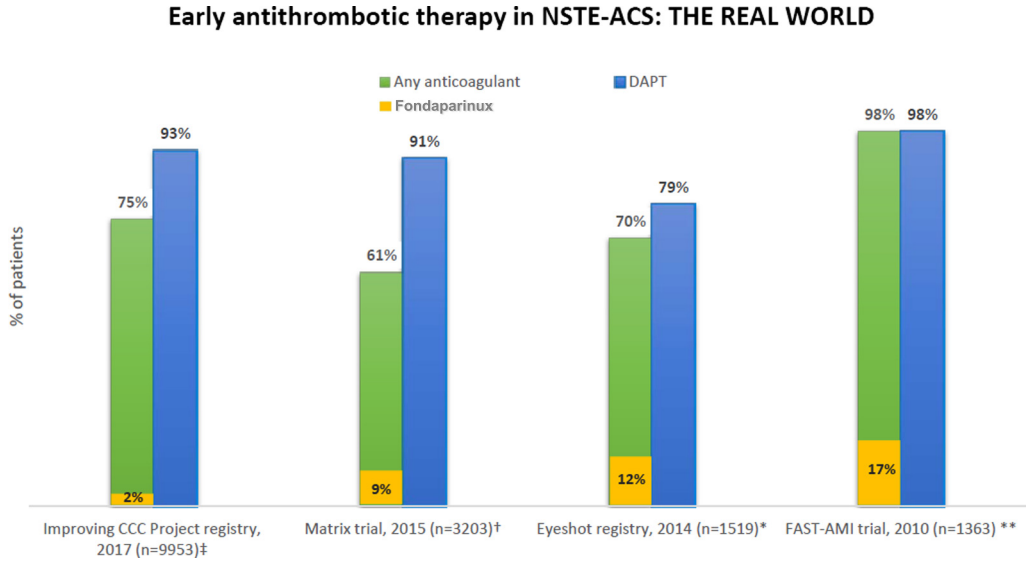


**Fig. 2.** Percentage of NSTE-ACS patients managed with dual antiplatelet therapy (DAPT) or anticoagulants in recent registries performed after 2010 and in the MATRIX trial, providing details on anticoagulant administration and timing in the early management of NSTE-ACS: Eyeshot registry (2014) [31]; Matrix trial (2015) [33]; the Improving CCC (Care for Cardiovascular Disease in China) ACS project registry (2017) [27], and FAST-AMI 2010 [28]. The percentage of patients receiving fondaparinux is indicated. * DAPT and anticoagulants before coronary angiography/during hospitalisation. † Medications administered before catheterisation. ‡ DAPT administered within 24 h of admission and parenteral anticoagulants used in the perioperative period. ** Medication in the first 48 h.

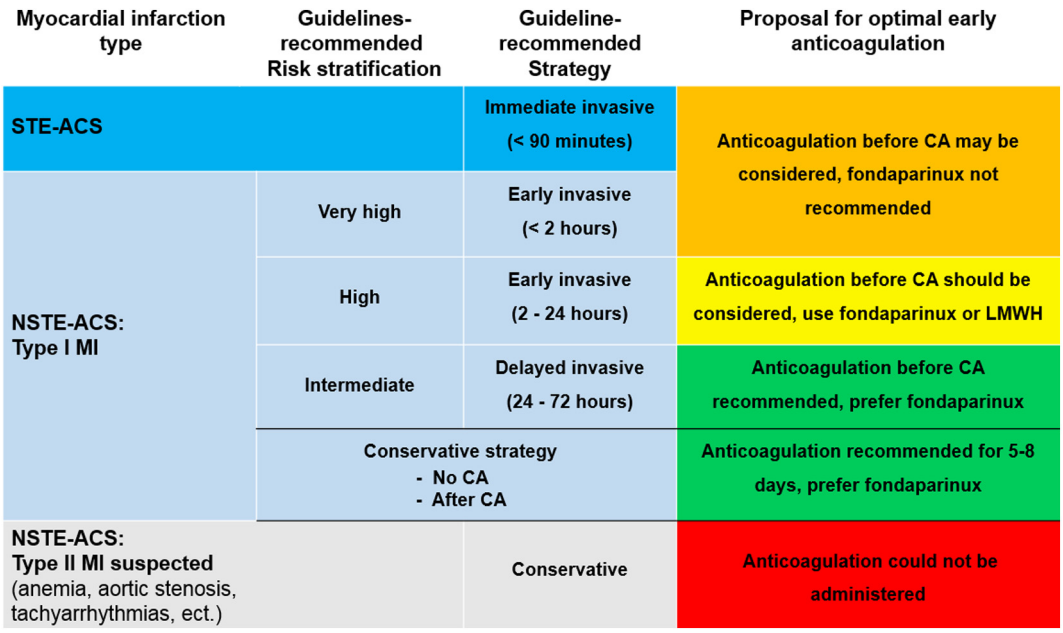


**Fig. 3.** Anticoagulation in the early management of different ACS presentations. We consider three main possible ACS clinical presentations: STE-ACS, NSTE-ACS type I MI, NSTE-ACS type II MI. Basing on the available evidence, we propose an early anticoagulant administration in NSTE-ACS type I MI tailoring by patient's risk and management strategy: -Guideline-definition of very high risk: guideline-recommended immediate invasive approach (<2 h, quasi STE-ACS NSTE-ACS). Proposal: anticoagulation may be considered; if used, prefer UFH and avoid fondaparinux. -Guideline-definition of high risk: guideline-recommended early invasive approach (<24 h). Proposal: fondaparinux or LMWH should be considered according to the patient's bleeding risk. -Guideline-definition of intermediate risk: guideline-recommended invasive approach within 72 h. Proposal: fondaparinux recommended. -Conservative approach: a conservative approach may be adopted directly or after CA. Proposal: in these patients, fondaparinux for 5–8 days is recommended according to the patient's bleeding risk. Early anticoagulation could also be used in the early phase of STE-ACS patients but fondaparinux should be avoided, as recommended by the very recent ESC guidelines. In patients with high probability of NSTE-ACS type II MI, early anticoagulation should we avoid and, when it is possible to reach an alternative diagnosis without performing CA, a direct conservative approach preferred.

concomitant ATT given in the early phase is lacking. We highlighted this in Fig. 1 evidencing a dichotomy in the investigation of antiplatelet and anticoagulant strategies.

### *4.2. International guidelines*

The latest guidelines from the (ESC) [6,26] and the AHA/ACC [7] strongly encourage early anticoagulation in NSTE-ACS (class I, LOE B for ESC and A or B for AHA/ACC) in addition to early dual antiplatelet therapy, even when potent P2Y12 inhibitors are employed (Class IIa, LEO C). This results in a course of triple ATT, a strategy linked to increased bleeding risk [41–43], whose efficacy/safety has never been compared to that of a dual ATT (either by DAPT or by a single antiplatelet agent in addition to an anticoagulant).

Interestingly, as the management of NSTE-ACS is becoming increasingly more similar to that of STE-ACS for high risk patients, a substantial divergence of recommendations in the use of anticoagulants is present. The 2017 ESC guidelines on STE-ACS [40] in fact, do not indicate a specific Class and LEO for the use of anticoagulation at the time of diagnosis, as recommended drugs to support primary PCI are UFH (class I, LOE A) or enoxaparin (class IIa, LOE A). Of note, fondaparinux has a Class I LEO A/B indication in NSTE-ACS guidelines and a Class III, LEO B indication in STE-ACS guidelines.

### *4.3. Contemporary clinical practice*

Several recent publications have re-evaluated the open questions pertaining to early anticoagulation in the management of NSTE-ACS [44,45]. In contemporary registries, adherence to the Guidelines strong recommendation for early anticoagulation ranges from 61% and 98%, whereas the overall high use of early DAPT may be linked to the currently short time interval from diagnosis to CA. In fact, there is a general trend in favor of pre-treatment with P2Y12 inhibitors to avoid stent thrombosis in modern management of NSTE-ACS [26]. The overall low use of fondaparinux in recent registries [27–29] may be attributed to: 1) association with increased catheter thrombosis rates mandating in every case routine full dose UFH administration during CA/PCI [46]; 2) data from the STE-ACS population indicating no ischaemic benefit of fondaparinux and a tendency towards increased bleeding [39]; 3) difficulty of monitoring its effect, as activated clotting time (ACT), routinely used in cath-labs, is not sensitive to fondaparinux, and 4) absence of a specific antidote (such as protamine for UFH) in case of procedural bleeding. Despite a strong class III Guideline negative recommendation, it should be noted that registries [12,35] show a high rate of heparins crossover, linked with an increased risk of bleeding [12]. In NSTE-ACS, the use of bivalirudin and GPIIb/IIIa is reported to be low [27–31].

In medically treated patients, subanalyses of both PLATO [21] and CURE [17] show, as in the overall trials, reduction ischaemic endpoints but higher bleeding rates when ticagrelor vs clopidogrel or clopidogrel vs placebo, respectively, are added to aspirin [17,21]. The TRILOGY trial [20] indicates no reduction in ischaemic endpoints but higher bleeding rates with prasugrel, as compared to clopidogrel, on top of aspirin in medically managed NSTE-ACS patients. Few data exist regarding the optimal length and efficacy of anticoagulation in association with powerful P2Y12 inhibitors (e.g., ticagrelor) in medically-managed NSTE-ACS. In conclusion, whether antiplatelet drugs combined with early anticoagulants enhance the benefit deriving from either treatment, or whether the same benefits are blunted by the increased bleeding risk of triple ATT, remains to be clarified both in conservative and invasively treated patients.

### *4.4. Tailoring anticoagulation type and timing to risk stratification: a proposal (Fig. 3)*

According to the reviewed data, we believe that the Guidelines-mandated, Class A, LEO A/B recommendation for early anticoagulation

in every NSTE-ACS scenario may be challenged. We hereby propose a distinction based on the type of MI according to the most recent MI classification [47], the conservative or invasive strategy chosen, and the time-frame of subsequent CA (if performed), taking also into account the specific anticoagulant used.

In our opinion, NSTE-ACS due to a primary coronary event (type I MI) should be grouped into three different risk categories, as notoriously proposed by ESC NSTE-ACS guidelines [6]. We propose a tailored approach to each group, according to the best available evidence (Fig. 3).

Both NSTE-ACS patients at very high risk (the so called "quasi STE-ACS" NSTE-ACS) and STE-ACS patients require a very early invasive approach (<2 h), but, as stated, the recommendation on early anticoagulation proposed by the respective ESC guidelines are very different. Although no evidence clearly supports early anticoagulant administration in NSTE-ACS patients rapidly undergoing CA [25,39] and early anticoagulation in STE-ACS is still debated [50], we believe a greater harmonisation of type and timing of anticoagulation could be reasonable in the light of the similar approach the two conditions require. Conversely, pathophysiological differences between STE-ACS and quasi-STE-ACS (including the generally larger coronary thrombus burden, the higher rate of single vessel disease and of total vessel occlusion in STE vs NSTE-ACS) are certainly present [2,3,48,49] and should be taken into account. According to pathophysiology [2,3,48,49] we speculate a potential minor effectiveness of early anticoagulation in terms of reduction of total vessel occlusion at initial angiography (the most convincing beneficial effect of early antiacoagulation in STE-ACS) in quasi-STE-ACS [51], since this condition is a priori less frequent in those patients [48,49]. Eventually, early anticoagulation may be considered in those patients, but fondaparinux should be avoided and UFH preferred, since intraprocedural UFH administration is invariably needed.

NSTE-ACS patients in the "high risk" category (typical troponin rise and fall or dynamic ECG changes or GRACE >140) should undergo an early invasive approach (<24 h) [6]. Evidence in support of early anticoagulation in these patients is scarce, and it is mainly represented by the SYNERGY trial [12]. We believe that the most consistent evidence in this setting is for fondaparinux (safer compared to LMWH) or, in alternative LMWH. However, we believe that their use is not mandatory and that the patient bleeding profile should be thoroughly considered.

Intermediate risk NSTE-ACS patients should undergo invasive management within 72 h. In these patients, the evidence in support of early anticoagulation is more convincing, even if RCTs evaluating placebo vs early anticoagulation when modern, powerful P2Y12 inhibitors are used, are lacking. Despite these limitations, the OASIS-5 trial [13] and the subsequent real-life analysis [34] support the use of fondaparinux with a relatively strong level of evidence.

A significant proportion of patients, even in a modern setting, undergo conservative management after CA or when CA is ruled out [31]. Although in type I conservatively-managed MI patients PCI is by definition not performed, these patients have (or are supposed to have, if CA is not performed) either thrombotic lesions or extremely severe, thrombus-prone coronary disease as the true cause of myocardial injury. In these patients, with the same limitations in evidence observed in intermediate risk patients, early anticoagulation (preferring fondaparinux on the basis of OASIS-5 trial [13]) should be recommended. The optimal duration of anticoagulation in medically treated patients is unknown. We recommend anticoagulation for 5–8 days according to several RCT that found no benefit in with longer anticoagulation [15]. For patients in which a conservative approach has been adopted because of a high bleeding risk or frailty, triple ATT should be adopted with extreme caution.

In NSTE-ACS type II MI patients, although the usefulness of revascularization is controversial, CA is often necessary to reach the diagnosis. We believe that in patients characterized by a low pre-test probability of type I MI (such as patients with anemia, aortic stenosis, tachyarrhythmias, ect,), early anticoagulant therapy could be avoided, since myocardial necrosis would not be linked to a primarily coronary event.

## 5. Conclusions

Evidence supporting the use of anticoagulant therapy in the early phase of NSTE-ACS is based on trials mostly performed in the 1990s. Subsequent RCTs have dichotomously tested antiplatelet or anticoagulant strategies separately, without a placebo arm. Since many innovations have occurred in the diagnosis and management of NSTE-ACS, such as the introduction of powerful oral platelet inhibitors and the high percentage of patients undergoing coronary angiography within a short time from diagnosis, the references cited by the guidelines to support the use of anticoagulants in the early phase of NSTE-ACS do not reflect contemporary real word practice, as also indicated by several registries. Interestingly, as the management of NSTE-ACS is resembling that of STE-ACS, especially for very high risk patients, a substantial divergence of recommendations in the use of anticoagulants is present in the respective guidelines, especially regarding fondaparinux. We provide a critical appraisal of the available evidence, and propose an early anticoagulation strategy tailored to the adopted management.

## Conflict of interest

Professor Andreotti reports receiving speaker or consultancy fees from Actelion, Amgen, Bayer, BMS/Pfizer, Boehringer-Ingelheim, Daiichi Sankyo and International Menarini Foundation.

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