EXPERT REVIEWS

Acute coronary syndromes: considerations for improved acceptance and implementation of management guidelines

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The management of acute coronary syndrome in Europe is covered by various European Society of Cardiology guidelines, which although valuable, are complex and may not always provide clear guidance in everyday clinical practice. Consequently, implementation of the guideline recommendations is frequently suboptimal. To complicate matters further, a wealth of new data from large trials examining novel anti-thrombotic agents will become or are already available, necessitating guideline updates. This article summarizes the gaps between current guideline-recommended treatment of acute coronary syndrome and daily practice as dictated by the evidence base, including recent trials. Reasons for the suboptimal implementation of the current European Society of Cardiology guidelines and possible solutions to making these more practice oriented are presented.

Keywords: acute coronary syndromes • antiplatelet agents • bleeding • coronary artery bypass grafting • guidelines • percutaneous coronary intervention • trials

The management of acute coronary syndromes (ACS) in Europe is currently covered by three sets of European Society of Cardiology (ESC) guidelines. Guidelines for non-ST-segment elevation ACS (NSTE-ACS) were produced in 2007 [1] and updated in 2011 [2]. The ST-segment elevation myocardial infarction (STEMI) guidelines issued in 2008 are still valid [3], and an update is planned for 2012. New joint ESC/European Association for Cardio-Thoracic Surgery guidelines on myocardial revascularization (incorporating percutaneous coronary intervention [PCI] and surgical aspects of coronary revascularization in acute and chronic conditions) were published in October 2010 [4]. These new guidelines already include recommendations on the use of the new oral antiplatelet agents, but recommendations will evolve as more clinical data become available. The aims of this review are to consider current and future recommendations for the management of patients with ACS, and to address potential reasons for the suboptimal implementation of ESC guidelines.

New oral antiplatelet agents

Prasugrel and ticagrelor are newly recommended in the latest ESC/EACTS revascularization guidelines, and in the updated NSTE-ACS guidelines. It is important to understand the differences in the mode of action, and even more important to understand the differences in the design of the clinical trials that have led to these recommendations.

Mode of action

The thienopyridines, prasugrel and clopidogrel, are both prodrugs with active metabolites that produce irreversible inhibition of $P2Y_{12}$ (ADP) receptors; however, prasugrel has greater efficacy due to a faster and more effective metabolism compared with clopidogrel [5]. The non-thienopyridine, ticagrelor, is a fast, direct-acting, reversible $P2Y_{12}$ inhibitor with a noncompetitive interaction with the $P2Y_{12}$ (ADP) receptor [6].

Platelet function tests are potentially valuable tools for predicting the clinical efficacy of antiplatelet therapy, and a case could be made

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for these to be performed for all new agents prior to clinical trials, although they are not recommended in routine practice because there is insufficient evidence of a clinically relevant benefit [7]. Indeed, recently the GRAVITAS trial showed no benefit for the combined ischemic end points with high-dose versus standard-dose clopidogrel in a high-risk patient population with high on-treatment platelet reactivity after PCI with a drug-eluting stent (DES), despite the use of functional testing as a trial dose selection identifier [8]. Prasugrel and ticagrelor result in higher levels of platelet inhibition and have faster onsets of action compared with clopidogrel at doses of both 300 and 600 mg [9–12], and this should translate into early protection against ischemic events in ACS patients with planned or performed PCI.

Differences in trial design & patient characteristics

Straightforward comparison of the clinical efficacy of clopidogrel, prasugrel and ticagrelor is limited by important differences in the trial designs used to test these agents (Table 1). The TRITON TIMI-38 trial [13], which demonstrated a clinical benefit of prasugrel compared with clopidogrel in moderate-to-high risk ACS patients with planned PCI, was designed before pretreatment with clopidogrel and the use of a high loading dose (≥600 mg) became standard practice in the USA. This study was more in line with US practice at the time, in which generally, patients were not pretreated with oral antiplatelet agents other than aspirin because of the greater use of early surgical coronary revascularization in ACS compared with Europe. Consequently, the TRITON TIMI-38 trial was designed to assess the effects of the study medication in treatment-naive PCI patients, a situation perhaps more akin to STEMI-ACS than non-ST-segment elevation myocardial infarction (NSTEMI) ACS. A total of 13,608 patients (10,074 with unstable angina [UA] or NSTEMI and 3534 with STEMI) were randomized to use either prasugrel or clopidogrel after angiography, or immediately after obtaining informed consent in STEMI patients with planned PCI. Patients who had received thienopyridines within 5 days prior to PCI were excluded, with the exception that STEMI patients were permitted to receive study medication before angiography. Nearly all patients (99%) had PCI at the time of randomization. The study drug was administered before the first coronary guidewire was placed in 25% of the patients. By contrast, the later CURRENT OASIS-7 [14] and PLATO [15] studies, which compared clopidogrel 300 versus 600 mg, and clopidogrel versus ticagrelor, respectively, randomized patients before angiography, and approximately a third of patients did not undergo PCI.

In addition to the variations in study design, small differences in the patient characteristics may have accounted for some of the differences in outcomes between the TRITON TIMI-38, CURRENT OASIS-7 and PLATO studies (Table 1) [13–15]. The proportion of patients with STEMI was greater in the PLATO study (37.7%) compared with the TRITON TIMI-38 (26.0%) and CURRENT OASIS-7 studies (29.2%), and the percentage of troponin-positive patients also differed between the studies (CURRENT OASIS-7 [65%]; TRITON TIMI-38 [75%] and PLATO [80%]). The PCI and coronary artery bypass grafting (CABG) rates were different between the studies; these are important factors that influence the outcome. In addition, a high rate of patients in the CURRENT OASIS-7 (20%) and PLATO (46%) studies were receiving clopidogrel treatment before randomization, either as a maintenance dose or a loading dose.

In contrast to the TRITON TIMI-38 trial, which showed a great early benefit and a less pronounced late benefit of prasugrel compared with clopidogrel [13], the end point–time curves for ticagrelor and clopidogrel in the PLATO trial demonstrated a great later divergence [15]. Clearly, variations in study design may account for these differences. The benefit of prasugrel compared with clopidogrel in the TRITON TIMI-38 trial was mainly driven by a decrease in nonfatal myocardial infarction (MI) and stent thrombosis. Most stent thrombosis in the ACS setting is observed in the first month [16]. The benefit of prasugrel compared with clopidogrel with regard to stent thrombosis is probably due to its more rapid onset, as study medication was given in the catheterization laboratory rather than as pretreatment. Interventional cardiologists may therefore favor prasugrel over ticagrelor based on the early benefits of prasugrel in the TRITON TIMI-38 study. However, in patients with a planned early invasive strategy in the PLATO study, ticagrelor did reduce stent thrombosis compared with clopidogrel, with similar reductions in the rates of stent thrombosis in bare-metal stents and DESs [17]. Only two-thirds of the PLATO study population underwent PCI, and over a third of the patients received a loading dose of clopidogrel prior to randomization, making an overall early benefit more difficult to detect.

Ticagrelor therapy demonstrated an unexpected but highly significant mortality benefit compared with clopidogrel therapy [15], which is not entirely explained by the antiplatelet effects or a reduction in major bleeds. It was highlighted that there was a trend towards reduced mortality with prasugrel compared with clopidogrel in the TRITON TIMI-38 study, which achieved statistical significance for STEMI patients [13]. Both ticagrelor and prasugrel increased thrombolysis in myocardial infarction major non-CABG bleeds compared with clopidogrel. It should be noted that the management of non-CABG patients differed between the TRITON TIMI-38 and the PLATO studies; in the TRITON TIMI-38 study all non-CABG patients underwent PCI, whereas this was not the case in the PLATO study. However, a subanalysis of the PLATO study patients with STEMI and planned PCI demonstrated similar results to those in the overall trial for major bleed rate [18].

Pooled data for clopidogrel compared with the newer agents described in patients who underwent PCI have been reported [19]. These indicated that the newer agents reduced mortality (by 15%) and stent thrombosis (by 40%) more than clopidogrel and had a reassuring safety profile, with an increased but nonsignificant risk of major bleeds; however, the limitations of these data, pooled from studies with different designs and different patient populations, were highlighted and the data require cautious interpretation. The efficacy and safety of prasugrel and ticagrelor have also been compared indirectly in a meta-analysis

Table 1. Summary of key points from the CURRENT-OASIS 7, PLATO and TRITON-TIMI 38 trials.

	CURRENT-OASIS 7 [14]	PLATO [15]	TRITON-TIMI 38 [13]
Trial design	Multinational, randomized, 2 × 2 factorial design study (double-blind for clopidogrel; open-label for aspirin)	Multinational, randomized, double-blind, parallel-group study	Multinational, randomized, double-blind, parallel-group study
Timing of randomization	Before angiography	Before angiography	After angiography
Study treatment	Double-dose clopidogrel: 600-mg loading dose on day 1, then 150 mg q.d. on days 2–7, then 75 mg q.d. on days 8–30, or Standard-dose clopidogrel: 300-mg loading dose on day 1, then 75 mg q.d. on days 2–30 and High-dose aspirin: 300–325 mg daily or Low-dose aspirin: 75–100 mg daily	Ticagrelor 180-mg loading dose, then 90 mg b.i.d. or clopidogrel 300-mg loading dose (only in patients who had not received an open-label loading dose, and had not taken clopidogrel for ≥5 days before randomization), then 75 mg q.d. Treatment duration: 6–12 months Patients undergoing PCI after randomization could receive (blinded) an additional dose of their study drug at the time of PCI: ticagrelor 90 mg or clopidogrel 300 mg All patients received aspirin 75–100 mg daily (unless not tolerated), following a 325-mg loading dose in those not already on aspirin	Prasugrel 60-mg loading dose, then 10 mg/day maintenance dose or clopidogrel 300-mg loading dose, then 75 mg/day maintenance dose Treatment initiated any time between randomization and 1 h after leaving the catheter laboratory (administered before first coronary guidewire placement in 25% of patients) Treatment duration: 6–15 months All patients received aspirin 75–162 mg daily
Patients (n)	25,086 with ACS managed with early invasive strategy NSTE-ACS 71% STEMI 29% Troponin positive 65%	18,624 hospitalized for ACS NSTE-ACS 59% STEMI 38% Troponin positive 80%	13,608 with ACS undergoing PCI NSTE-ACS 84% STEMI 26% Troponin positive 75%
PCI/CABG (%)	PCI: 69; CABG: 7	PCI: 64; CABG: 10	PCI: 99; CABG: 1
Clopidogrel before randomization (%)	20	46	26 before PCI (patients treated with thienopyridines ≤5 days prior to PCI were excluded, except STEMI patients were permitted to receive study medication before angiography)
Primary end point (definition)	Composite: death from CV causes, MI (or reinfarction) or stroke	Composite: death from vascular causes, MI or stroke	Composite: death from CV causes, nonfatal MI or nonfatal stroke
Primary end point (result)	At 30 days: double-dose clopidogrel 4.2% vs standard-dose clopidogrel 4.4% (HR: 0.94; 95% CI: 0.83–1.06; p = 0.30)	At 12 months: ticagrelor 9.8% vs clopidogrel 11.7% (HR: 0.84; 95% CI: 0.77–0.92; p < 0.001)	At 15 months: prasugrel 9.9% vs clopidogrel 12.1% (HR: 0.81; 95% CI: 0.73–0.90; p < 0.001)
CV death	Double-dose clopidogrel 2.1% vs standard-dose clopidogrel 2.2% (HR: 0.95; 95% CI: 0.81–1.13; p = 0.57)	Ticagrelor 4.0% vs clopidogrel 5.1% (HR: 0.79; 95% CI: 0.69–0.91; p = 0.001)	Prasugrel 2.1% vs clopidogrel 2.4% (HR: 0.89; 95% CI: 0.70–1.12; p = 0.31)
Death from any cause	Double-dose clopidogrel 2.3% vs standard-dose clopidogrel 2.4% (HR: 0.96; 95% CI: 0.82–1.13; p = 0.61)	Ticagrelor 4.5% vs clopidogrel 5.9% (HR: 0.78; 95% CI: 0.69–0.89; p < 0.001)	Prasugrel 3.0% vs clopidogrel 3.2% (HR: 0.95; 95% CI: 0.78–1.16; p = 0.64)
Bleeding	TIMI major bleeding: Double-dose clopidogrel 2.5% vs standard-dose clopidogrel 2.0% (HR: 1.24; 95% CI: 1.05–1.46; p = 0.01)	TIMI major non-CABG bleeding: ticagrelor 2.8% vs clopidogrel 2.2% (HR: 1.25; 95% CI: 1.03–1.53; p = 0.03)	TIMI major non-CABG bleeding: prasugrel 2.4% vs clopidogrel 1.8% (HR: 1.32; 95% CI: 1.03–1.68; p = 0.03)

ACS: Acute coronary syndrome; b.i.d.: Twice daily; CABG: Coronary artery bypass grafting; CV: Cardiovascular; HR: Hazard ratio; q.d.: Once daily; MI: Myocardial infarction; NSTE-ACS: Non-ST-segment elevation acute coronary syndrome; PCI: Percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; TIMI: Thrombolysis in myocardial infarction.

of three clinical trials [20]. The investigators found that the drugs were similar in terms of efficacy (overall death, MI, stroke or their composite) and safety. However, prasugrel was associated with a significantly lower risk of stent thrombosis, while ticagrelor was associated with a significantly lower risk of any major bleeding and bleeding associated with CABG. Major bleeding not related to CABG was similar with both drugs. It should also be noted that one possible reason why ticagrelor reduced mortality and prasugrel did not is that mortality reduction was pronounced in patients assigned to conservative treatment in the PLATO study; there were no patients assigned to conservative treatment in the TRITON TIMI-38 trial. A beneficial effect of higher tissue levels of adenosine, due to the inhibition of re-uptake by ticagrelor, has also been proposed as a possible explanation for the survival benefit witnessed with this drug [17]. Furthermore, the slope of the event curve suggests the impact of factors beyond the acute stenting period, unlike the curve in the TRITON TIMI-38 study.

Individual patient response

With the availability of new agents, it is important to understand whether or not to tailor treatment to individual patients, and how best to do this. Importantly, there is accumulating evidence that the *CYP2C19* genotype determines a patient's response to clopidogrel. A recent meta-analysis has indicated an increased risk of stent thrombosis, MI and death in heterozygotes as well as homozygotes for the *CYP2C19* loss-of-function allele treated with clopidogrel [21]. These data suggest that approximately a third of ACS patients could be poor responders to clopidogrel. By contrast, a study in 5059 patients with ACS or atrial fibrillation from two large randomized trials showed a consistent benefit of clopidogrel versus placebo regardless of *CYP2C19* status [22]. Further research indicates that specific *CYP2C19* haplotypes may be associated with varying effects on clopidogrel activity [23]. Interestingly, in the European population, there is a relatively common gain-of-function variant of *CYP2C19*, which may identify patients with significantly higher risk of bleeding after treatment with clopidogrel [24].

Prasugrel and ticagrelor are not affected by the *CYP2C19* genotype, resulting in the same event rate in carriers and noncarriers [25,26], so they may be alternative treatment options for patients carrying high-risk variants. Whether all patients should be genotyped prior to treatment with clopidogrel, and whether newer agents should be reserved for nonresponders, are important questions, given the recent US FDA-boxed warning [101], and the American College of Cardiology/American Heart Association (ACC/AHA) clinical alert on clopidogrel use [7]. The cost–efficacy argument of using the cheaper clopidogrel in all patients but those shown to have suboptimal response, albeit with the increased expense of testing, needs to be considered. In the absence of testing, selected high-risk groups such as those undergoing left main stem stenting may be best treated with agents such as prasugrel or ticagrelor, in cases where stent thrombosis, if it were to occur, would have significant consequences.

The presence of diabetes as a comorbidity in ACS patients may also affect medical management options. The TRITON TIMI-38 trial demonstrated a benefit of prasugrel over clopidogrel in patients with diabetes without excess of bleeding [13]. By contrast the PLATO [15,27] and CURRENT OASIS-7 studies [14] did not show a statistically significant reduction in events compared with clopidogrel at usual doses in patients with known diabetes treated with ticagrelor or high-dose clopidogrel. Consequently, prasugrel may be the preferred treatment option in ACS patients who have diabetes. Chronic kidney disease (CKD) is also a powerful marker of risk in ACS, including both ischemic and bleeding events. Of interest, CKD patients drew an impressive benefit from ticagrelor in the PLATO study, with a 23% relative risk reduction of the primary ischemic end point (compared with a nonsignificant 10% reduction in patients without CKD), and an even more striking 4.0% absolute and 28% relative risk reduction of all-cause mortality [28].

There are a lack of data on anti-thrombotic therapies given to patients with UA, including those presenting with chest pain not caused by troponin-positive ACS. Use of such agents in these latter patients may place them at increased risk of major bleeds without providing any clinical benefit. It is also unknown whether the more potent anti-thrombotic agents are equally effective in patients with UA compared with patients with positive markers of necrosis. New registries should provide data on clinical outcomes, including bleeding complications, in these patients.

Unlike prasugrel [13], ticagrelor appears not to increase bleeding risk in low-bodyweight patients and the elderly [15], and there is no warning about its use in such patients. Low response to antiplatelet therapy in the elderly is an important issue [29]; there is considerable variability in responses to clopidogrel [30], with older age, higher BMI and diabetes mellitus identified as possible risk factors for nonresponse in ACS [31]. However, ticagrelor and prasugrel have not shown benefits compared with clopidogrel in elderly patients [13,15].

Duration of therapy

The optimal duration of antiplatelet therapy also needs consideration. To date, regulatory bodies indicate that the duration should be 1 year, based on the CURE trial. Thus far, longer term duration has been proposed but not well studied. Several ongoing trials are examining the balance between reduction in stent thrombosis and increased risk of severe bleeding with long-term use of antiplatelet therapies in patients who underwent PCI with stenting in the acute phase. Results are available from a Korean study in which ACS patients free of major adverse cardiac or cerebrovascular events and major bleeding for ≥12 months after implantation of DESs were randomized to clopidogrel plus aspirin or aspirin alone [32]. After 2 years, there was no difference between the groups in terms of cumulative risk of an event (MI or cardiac death), indicating that clopidogrel can be stopped after 12 months of treatment. Indeed, a trend towards a higher rate of events with longer term clopidogrel therapy suggested that continuing clopidogrel beyond this period may be detrimental. Korean patients may be poor metabolizers of clopidogrel, possibly because of a higher prevalence of the *CYP2C19* polymorphism compared with Caucasians [33]; this limits the

applicability of these data to other populations. In addition, the statistical power of this study is questionable given the low rate of MI and stent thrombosis, and the 'play of chance' cannot be excluded. The PRODIGY study, presented at the ESC Congress in 2011 (Paris, France), also found that 2 years of clopidogrel treatment after coronary stenting did not reduce the ischemic event rate compared with 6 months of clopidogrel treatment, but doubled the risk of major bleeding [102].

The ISAR-SAFE (ClinicalTrials.gov identifier: NCT00661206 [34,103]) and the DAPT (ClinicalTrials.gov identifier: NCT00977938 [35,103]) trials should definitively determine the optimal timing of discontinuing clopidogrel after stent implantation. Pooled data from long-term (≥1 year) clopidogrel trials suggest that cardiovascular mortality is higher in coronary patients who continue clopidogrel for more than 1 year [36]. This may be determined by prothrombotic state, which is high initially but decreases with time. Long-term studies are currently ongoing to examine the effects of ticagrelor (PEGASUS; ClinicalTrials.gov identifier: NCT01225562 [103]) and prasugrel (TRILOGY ACS; ClinicalTrials.gov identifier: NCT00699998 [37,103]) in nonintervention patients. The current guidelines recommend 1 year of dual antiplatelet therapy after ACS, irrespective of stent placement [4].

Implications for guidelines

Current recommendations on the use of clopidogrel can still be considered valid [4]. The data on the efficacy of prasugrel and ticagrelor look promising. However, as referred to above, the TRITON TIMI-38 trial does not reflect standard clinical practice in many centers in Europe, although it may be applicable to STEMI where preloading time is short. Furthermore, real-life patients differ from those in clinical trials, and continued surveillance of the benefits and risks of newer agents is vital. Physicians may find it difficult to choose between prasugrel and ticagrelor based on their benefits in STEMI patients, and more prescriptive guidelines are called for. Without head-to-head comparisons of prasugrel and ticagrelor, or studies of identical design comparing them with clopidogrel, there are currently insufficient data to determine whether differences in efficacy exist between these two agents. New ESC STEMI guidelines are anticipated in 2012, and should provide updated recommendations on oral antiplatelet agents. For NSTE-ACS, the updated ESC guidelines recommend the use of ticagrelor for all patients and moderate-to-high risk of ischemic events, regardless of initial treatment strategy [2]. Unless there are contraindications, they recommend prasugrel for $P2Y_{12}$ inhibitor-naive patients (especially diabetics) with known coronary anatomy and who are proceeding to PCI [2].

Anticoagulant agents

Intravenous & subcutaneous anticoagulants

There is ongoing debate regarding the best choice of parenteral or subcutaneous anticoagulant therapy for acute-phase management of ACS patients. Current recommendations for the use of unfractionated heparin (UFH), enoxaparin, fondaparinux or bivalirudin vary depending on whether or not patients are undergoing fibrinolysis, PCI or surgical revascularization, and on individual patient characteristics, including ischemic and bleeding risks.

UFH is still widely used, but a systematic overview of enoxaparin studies involving NSTE-ACS patients (with or without PCI) showed a statistically significant reduction in the composite end point of death or nonfatal MI at 30 days with enoxaparin compared with UFH [38]. Furthermore, individual responses to UFH vary considerably, necessitating careful monitoring of activated clotting times [39]. In STEMI populations, trials showed that enoxaparin reduced cardiovascular event rates compared with UFH in patients receiving fibrinolysis [40] or undergoing primary PCI (ATOLL trial) [41] but not in those who were unsuitable for revascularization (TETAMI trial) [42]. There is also evidence of an increased risk of bleeding with enoxaparin compared with UFH (e.g., the EXTRACT-TIMI 25 study [43], the TIMI 11B-ESSENCE meta-analysis [40] and the SYNERGY trial [44]). It should be noted that pre-randomization anticoagulation treatment in these trials may have led to an excess of bleeding in some cases. Nevertheless, careful dose adjustment of enoxaparin and other low-molecular-weight heparins is necessary in patients who are older, underweight or have renal failure. Both UFH and low-molecular-weight heparins carry a potential risk of 'heparin rebound' after stopping treatment, resulting in increased thrombin generation (i.e., above baseline levels), but this tends not to be a serious clinical issue. Heparin-induced thrombocytopenia is an uncommon but serious complication [39].

The selective Factor Xa inhibitor fondaparinux has been shown to achieve a comparable reduction in cardiovascular events to that achieved with enoxaparin in patients with NSTE-ACS, with a significant reduction in major bleeding, leading to improved long-term mortality and morbidity, in the fondaparinux group (OASIS-5 trial) [45]. Although the bleeding rates due to dose choice of enoxaparin were higher than in previous studies with this agent, similar results were seen in a secondary analysis of patients in this study who underwent PCI [46]. However, guiding catheter thromboses were more common in the fondaparinux group compared with enoxaparin (0.9 vs 0.4%), except in those who also received open-label UFH after fondaparinux [46]. In a study in STEMI patients, fondaparinux was found to reduce cardiovascular end points compared with placebo in those without an indication for heparin, and compared with UFH in those with an indication for heparin, with no differences in major bleeding between the treatment groups (OASIS-6 trial) [47]. It should be noted that most patients who did not undergo primary PCI in this study were treated with streptokinase, and only a minority were treated with fibrin-specific agents. As in the OASIS-5 trial, there was an increased rate of guiding catheter thrombosis with fondaparinux compared with UFH in patients undergoing PCI. A Cochrane Database systematic review of fondaparinux randomized controlled trials (RCTs) in patients with ACS found that fondaparinux was associated with a reduced risk of all-cause mortality at 90–180 days compared with UFH or enoxaparin, and with a reduced incidence of major and minor bleeding compared with enoxaparin (but not UFH) [48].

Bivalirudin is a direct thrombin inhibitor that has demonstrated comparable efficacy to heparin (UFH or enoxaparin) plus a GPIIb/IIIa inhibitor in NSTE-ACS patients, including those undergoing PCI, with similar rates of major bleeding (ACUITY trial) [49,50]. Bivalirudin was associated with a significant reduction in major bleeding, compared with heparin and a GPIIb/IIIa inhibitor, with similar rates of ischemic end points. Subsequent analysis of PCI patients from the ACUITY trial suggested that the timing of clopidogrel therapy was important in this context [51]. That is, bivalirudin without a GPIIb/IIIa inhibitor may actually be associated with worse outcomes than are associated with heparin in patients who only received clopidogrel more than 30 min after PCI or not at all, as opposed to before or within 30 min of PCI. On the other hand, bivalirudin may be particularly suitable for elderly patients with NSTE-ACS because bleeding complications were significantly less frequent in patients aged 75 years or more treated with bivalirudin alone, compared with heparin plus a GPIIb/IIIa inhibitor, but with similar rates of ischemic outcomes [52]. In the recently published ISAR-REACT 4 study in NSTEMI patients undergoing PCI, bivalirudin was also found to be associated with significantly less bleeding than heparin plus abciximab, with comparable ischemic event rates [53].

A study evaluating bivalirudin in STEMI patients undergoing PCI also demonstrated comparable efficacy and reduced rates of major bleeding compared with UFH plus a GPIIb/IIIa inhibitor (HORIZONS-AMI trial) [54]. Patients treated with a clopidogrel 600-mg loading dose in this study had significantly reduced 30-day ischemic adverse and bleeding event rates compared with those who received a clopidogrel 300-mg loading dose [55]. The 3-year mortality rate was significantly reduced in bivalirudin-treated patients [56].

New oral anticoagulants

The oral Factor Xa inhibitors rivaroxaban, apixaban and darexaban have all been evaluated on top of standard therapy in ACS, with varying degrees of benefit and a consistent increase in bleeding risk versus placebo. Development of darexaban has actually been discontinued for all indications [104], following disappointing results in a Phase II trial in ACS, which showed increased bleeding with no reduction of ischemic events with various darexaban regimens on top of dual antiplatelet therapy (RUBY-1 trial) [57].

A Phase III trial with apixaban in ACS was terminated prematurely after enrollment of 7392 patients (out of a planned 10,800), because of an increased bleeding risk with apixaban versus placebo, with no reduction in recurrent ischemic events (APPRAISE-2 trial) [58]. A Phase II Japanese study (ClinicalTrials.gov identifier: NCT00852397 [103]) with apixaban has also been stopped.

The oral direct thrombin inhibitor dabigatran has also been evaluated in a Phase II study in ACS patients, but showed a dose-related increase in major bleeding at 6 months without a convincing signal for a reduction in ischemic events (RE-DEEM trial) [59].

However, a Phase III trial with rivaroxaban in ACS reported a statistically significant reduction in the primary composite end point of cardiovascular death, MI and stroke compared with standard therapy plus placebo (ATLAS ACS 2-TIMI 51 trial) [60]. The low-dose rivaroxaban arm (2.5 mg twice daily) showed a significant reduction in total mortality. There was an increased risk of major and intracranial bleeding with rivaroxaban, but no increased risk of fatal bleeding.

Implications for guidelines

The latest ESC guidelines for NSTE-ACS recommend the use of fondaparinux as a first-line anticoagulant, because it has the best efficacy–safety profile [2]. For patients undergoing PCI, they also recommend the use of a single bolus of UFH. Subsequent choices are enoxaparin and then UFH, although bivalirudin without a GPIIb/IIIa inhibitor is recommended as an alternative for patients with an early invasive strategy, particularly if the bleeding risk is high [2]. The current STEMI guidelines also recommend UFH or bivalirudin during primary PCI. Whether rivaroxaban on top of dual antiplatelet therapy will be recommended in future guidelines will depend on further analyses of the ATLAS ACS 2 study.

Shortcomings of current guidelines

Practical issues

Current guidelines do not always reflect the practical issues of everyday clinical practice. Although the pocket guides produced from the guidelines are a useful resource to guide treatment decisions, there is a need for more prescriptive guidelines incorporating treatment algorithms with a clear hierarchy of therapies, rather than a 'menu' from which treatments can be chosen. Future guidelines should also include consideration of the advantages and disadvantages of different risk score models (e.g., TIMI vs GRACE) [61]. There is also not enough information on the use of bleeding risk scoring systems.

In general, clearer guidance on the timing of intervention is required. For NSTE-ACS, however, this has been taken care of in the new joint revascularization guidelines, which recommend variable timing of intervention depending on risk [4]. In high-risk patients (e.g., with a GRACE risk score >140), they recommend urgent angiography within 24 h. In lower risk subsets of NSTE-ACS patients, however, they recommend that angiography and subsequent revascularization should be performed within 72 h of admission. It should be remembered that this 72 h was from time of randomization in the trials and therefore may indeed be longer (up to 96 h, as suggested by the UK National Clinical Guidelines Centre ACS guidance) [105]. The updated ESC guidelines for NSTE-ACS also provide a useful step-by-step guide for the assessment and management of patients presenting with symptoms suggestive of ACS [2].

Genotyping & platelet function

Recommendations should be provided on the usefulness of testing patients before starting antiplatelet therapy. Consideration should be given to the value of genotyping, assessment of platelet

response and determination of risk factors [7,8,101]. The relative cost–effectiveness of performing genetic testing, and then the appropriate use of the newer, more expensive agents in clopidogrel low responders, versus using newer agents in all patients, should be evaluated and may determine the recommended treatment strategy. Moreover, a better definition of low responders for clopidogrel is required to guide the choice of alternative therapies.

Bleeding risk

Bleeding in ACS patients is an important issue, as emphasized by the ESC. Late bleeding is not generally observed by interventional cardiologists, and its importance should therefore be highlighted in the guidelines. A new bleeding score for patients with ACS undergoing PCI has been developed [62], based on data from the ACUITY [63] and HORIZONS studies [54]. Others, such as the CRUSADE [64] bleeding score, which apply to patients with NSTE-ACS, are also available. However, these are rarely used in clinical practice, and specific recommendations to use them have been included in the most recent ESC NSTE-ACS guidelines [2]. A new classification of the severity of bleeding complications, the BARC definition, is now available [65]. Consideration was given to the limitations of some of the classical historical definitions but also to capture bleeding events that are meaningful to patients and impact clinical outcomes. Definitions of bleeding are based on consensus and remain practical and easy to implement. The importance of bleeding on medium- and late-term mortality still does not feature in many cardiovascular physicians' thinking. Whether or not an acute intervention is performed, there remains a significant risk of bleeding during the year following an ACS. A detailed analysis of causes of bleeding and the possible interruption of antithrombotic treatment is currently being performed in the EPICOR registry (ClinicalTrials.gov identifier: NCT01171404 [103]).

Secondary prevention of cardiovascular disease

More emphasis should be given in the guidelines to the secondary prevention of cardiovascular disease, and the benefits of long-term use of statins and management of diabetes mellitus should be highlighted [66].

Definitions for classes of recommendations & levels of evidence

Guidelines are evidence-based, and are the result of the scientific analysis of available data. Therefore, not all patient groups can be included in guidelines because of the lack of clinical data in certain patient populations. As a result, guideline committees can make recommendations but do not replace medical experience; nevertheless, clinical practice based on guidelines rather than clinical judgment alone is associated with better patient outcomes [67]. Swedish registry data have shown that increasing adoption of evidence-based treatments for STEMI from 1996 to 2007 resulted in significant decreases in in-hospital, 30-day and 1-year mortality during that period ($p < 0.001$ in each case) [67].

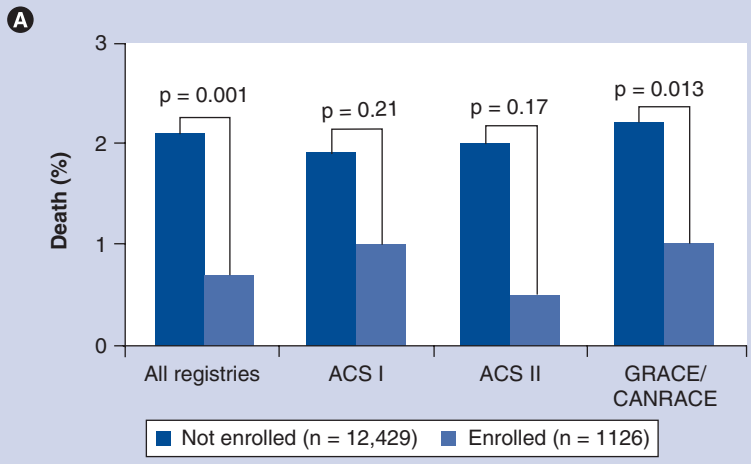
Definitions for classes of recommendation and levels of evidence on which guidelines are based were originally developed in the USA, and were adopted by the ESC. These definitions may no longer meet the requirements of current clinical studies. They are complex and may be interpreted differently by guideline committees. In addition, there is a large difference between class IA (strong evidence) and class IC (expert consensus), but this may not be easily recognized by guideline users. A simpler set of definitions for the classes and levels may be achieved by the removal of class III (referring to this, instead, as a contraindication), by a focus on consensus or divergence of opinion, by emphasis on studies with primary clinical or surrogate end points and, importantly, by taking the power of the trial into consideration.

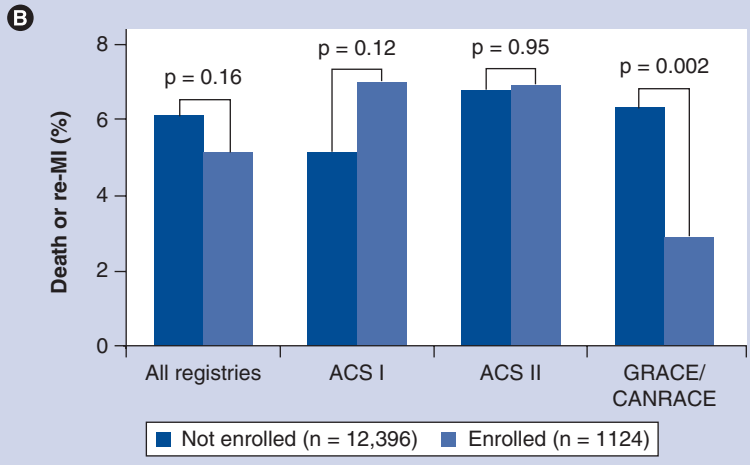
The best level of evidence (level A or B) comes from RCTs, but too many recommendations in guidelines are based on level C evidence. More RCTs with adequate power and a primary clinical end point are therefore required. One possibility is for clinical trials to be given an evidence-based medicine score, based on factors such as whether they were double-blind, measured a clinical or surrogate primary end point, and the statistical power of the study [68]. While surrogate end points can be informative, studies with clinical outcomes as the primary end point should be given priority. The guidelines should emphasize where further RCT data are required and its potential impact.

Implementation of guidelines

Implementation of the guidelines remains a major challenge, requiring substantial dissemination of education. A number of large registries (including GRACE [69], DESCARTES [70,71], MACARA [72], CRUSADE [73], the Euro Heart Survey [EHS] [74] and ATPOR [75]) have demonstrated variable adherence to guidelines for the management of patients with ACS, although there have been improvements over the years [76]. Programs promoting evidence-based guidelines, such as the GAP initiative [77], CRUSADE [73] and 'Get With The Guidelines' [78,79], have demonstrated that it is possible to improve quality of care. EQUIP-ACS is a cluster-randomized trial that compared an education program to improve the quality of care in patients with NSTE-ACS with no intervention in 38 hospitals from five European countries [80,81]. The results showed that a quality improvement intervention can improve the results of patients measured by quality indicators [81].

One problem is that too many guidelines exist within overlapping areas (such as the three sets of ESC guidelines for ACS mentioned above). They are sometimes inconsistent, which creates confusion and gives the perception that they are based on opinion rather than fact. Such inconsistency is a possible barrier to the implementation of guideline recommendations. In addition, updating the guidelines too frequently may create confusion and hinder their adoption. Updates should be timed to reflect quantum steps in important breakthroughs in treatment. It is also important to verify how treatment guidelines are being used in clinical practice, and to monitor the effect of guideline implementation by means of registries. As described earlier, for example, there was a clear association between the evidence-based changes in Swedish management strategy over time and improvement in clinical outcome for STEMI patients [67].





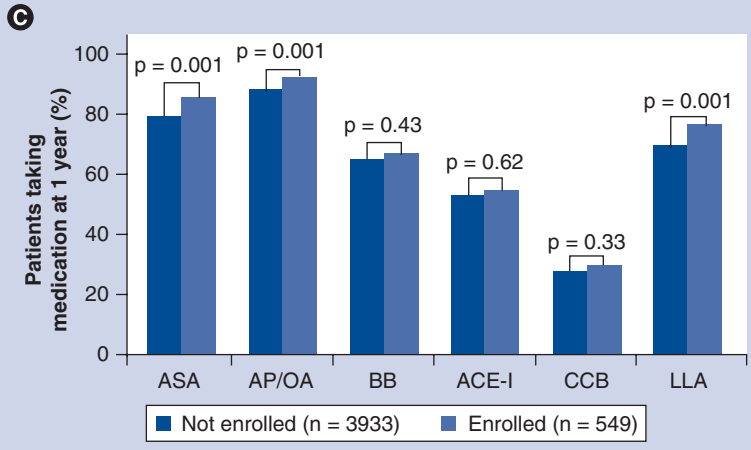


Figure 1. Comparison of in-hospital adverse events and 1-year medication use in patients with non-ST-segment elevation ACS† according to whether they were not enrolled or enrolled in clinical trials. (A) death, **(B)** death and/or re-MI, **(C)** 1-year medication use.
†Data taken from the Canadian ACS I (1999–2011), ACS II, (2002–2003), GRACE (2004–2007) and CANRACE (2008) registries, which included 13,566 patients with non-ST-segment elevation ACS, of whom 1126 (8.3%) participated in clinical trials.
ACE-I: ACE inhibitor; AP/OA: Antiplatelet/oral anticoagulant; ASA: Acetyl salicylic acid; BB: β-blocker; CCB: Calcium-channel blocker; LLA: Lipid-lowering agent; re-MI: Recurrent myocardial infarction.
Reproduced with permission from [83].

European versus national guidelines: do we need both?

European countries differ greatly in terms of clinical practices and healthcare systems. Some countries produce national guidelines, which may contain recommendations that differ from those in the ESC guidelines, particularly if routine clinical practice differs from the standard of care used in RCTs. One example is the difference in the timing of intervention for NSTEMI in the UK guidelines versus that in the European guidelines. National guidelines may also be necessary to account for local cost–effectiveness considerations. Local physicians' 'ownership' of national guidelines may also help their implementation, and national guidelines may improve implementation when patient care is shared between specialties (e.g., acute care physicians, anesthesiologists and cardiovascular surgeons).

Many countries have moved towards the endorsement and implementation of ESC guidelines, with amendments or annotations appropriate for the local area, rather than producing national guidelines. It may be useful to consider ideas from national guideline committees when developing the ESC guidelines. It is standard procedure for one representative per national society to participate in the review process for the ESC guidelines, which allows for input of local considerations.

Registry data in ACS

Low implementation of guidelines

Owing to case selection, there is a gap between treatment and outcomes in RCTs and those in real-life clinical practice. In most cases, even patient registries may reflect selection bias (unless they contain sequential all-comer cases), and show better management performance and outcomes compared with real life. Nevertheless, registry data provide a more realistic representation of current practices than RCT patient populations, which are highly selected and exclude many patients with comorbidities that place them at high risk. Consequently, early mortality rates may be as much as three time higher in registries than in RCTs, with higher rates of death/reinfarction, and lower rates of medication use (Figure 1) [82].

Registry data have indicated a trend for decreasing mortality in STEMI patients [83]. In recent years mortality rates have changed little in NSTE-ACS patients, but rates of heart failure have fallen [83]. Data from the EHS ACS-III

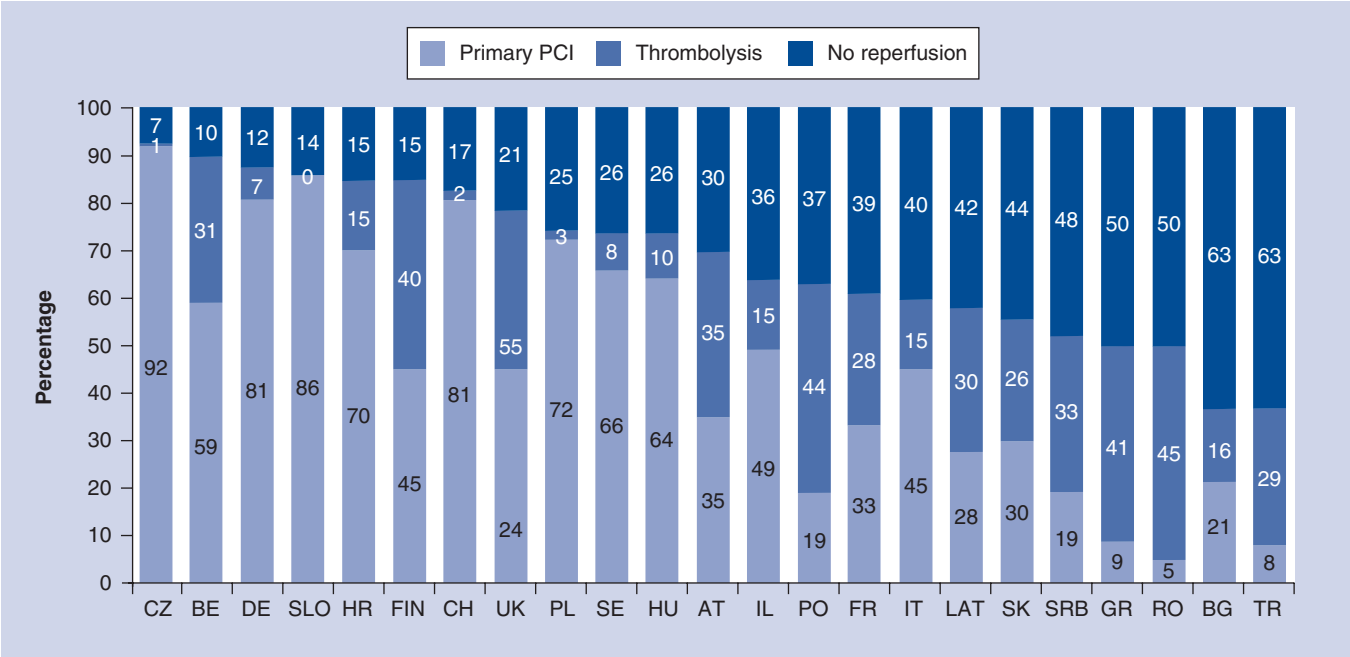


Figure 2. Hospitalized ST-elevated myocardial infarction treatment in Europe (data from national registries or surveys).
100%: all hospitalized STEMI patients in each given country; light blue color: STEMI patients treated by primary PCI; blue color: STEMI patients treated by thrombolysis; dark blue color: STEMI patients not treated with any reperfusion.
AT: Austria; BE: Belgium; BG: Bulgaria; CH: Switzerland; CZ: Czech Republic; DE: Germany; FIN: Finland; FR: France; GR: Greece; HR: Croatia; HU: Hungary; IL: Israel; IT: Italy; LAT: Latvia; PCI: Percutaneous coronary intervention; PL: Poland; PO: Portugal; RO: Romania; SE: Sweden; SK: Slovakia; SLO: Slovenia; SRB: Serbia; TR: Turkey; UK: United Kingdom.
Reproduced with permission from [86].

show that catheterization and PCI have increased, while the use of fibrinolysis has decreased [84]. The use of evidence-based therapies for ACS has increased over time but they are still underused. A recent review of national registry data in Europe showed that, on average, approximately a third of STEMI patients do not receive reperfusion therapy (ranging from 7 to 63% across 30 countries; Figure 2) [85]. The expanded GRACE registry showed that even well-established therapies for secondary prevention, such as β-blockers and statins, are underused, although there have been increases in the use of such agents in recent years [76]. Data from the GRACE registry suggested that there had been no reductions in the time to primary PCI or fibrinolysis for STEMI patients between 2003 and 2007 [86], although EHS ACS-III data indicate some improvement between 2006 and 2008 [84]. Nevertheless, a reduction in the time to reperfusion is still needed in clinical practice to improve outcomes. These registry data demonstrate that guideline recommendations do not always translate into changes in real-life clinical practice. Indeed, these data may be significantly out of date by now, thus continued reports on real-life outcomes and metrics are essential.

Guidelines recommend objective risk assessment to guide the selection of patients for invasive treatment. However, this is performed infrequently, and risk stratification of patients, including assessment of vascular anatomy, is poor. High-risk NSTE-ACS patients are undertreated, and low-risk patients receive unnecessarily aggressive therapy [70]. Availability of a catheterization laboratory, rather than risk, is the main predictor of early PCI [72,87–90]. Moreover, high-risk markers (e.g., older age, diabetes and renal disease) and female gender are key factors predicting that a patient will tend not to undergo PCI. Failure to treat high-risk patients according to guidelines may be associated with poorer outcomes [91], and may partially explain why real-life outcomes are worse than those in RCTs. Lack of credibility of the data on which the guidelines are based may be a contributing factor for poor adherence to the recommendation of treatment according to objective risk assessment.

Indeed, the EHS ACS III registry showed that nearly 30% of patients presenting with ACS are older than 75 years [84]. Regardless of the type of ACS, elderly patients have excess mortality and increased risk of bleeding complications. The registry demonstrated that in elderly patients presenting with ACS, fewer guideline-recommended medications (including aspirin and clopidogrel) are used than in younger patients. Furthermore, invasive treatment is used less frequently in the elderly population. This approach leads to exclusion of patients who may have significantly higher risk reduction by an invasive approach, and recent data support the implementation of early invasive strategies in elderly patients with ACS, especially in NSTEMI. Analysis of data from patients enrolled in the German Acute Coronary Syndromes Registry showed that invasive strategy is superior to medical therapy in reduction of in-hospital (odds ratio: 0.55; 95% CI: 0.35–0.86) and 1-year mortality (odds ratio: 0.56; 95% CI: 0.38–0.81) rates [92]. Excluding subgroups of patients from trials – especially those

who are at higher risk but who nevertheless do better with treatment, even if it is invasive – disadvantages whole swathes of the patient population.

Role of the cardiovascular surgeon

PCI versus CABG

Recent studies have demonstrated that, although ACS patients undergoing PCI demonstrate increased survival and lower morbidity in the short term compared with patients undergoing CABG, longer term survival and morbidity are often better in CABG patients [93,94]. However, it should be noted that CABG is often delayed and performed in lower risk patients while patients who undergo PCI are more likely to have STEMI, cardiac arrest or cardiogenic shock, and are more likely to undergo revascularization on the day of admission compared with CABG-treated patients. CABG is associated with an increased risk of nonfatal bleeding, which increases the risk for transfusion, infection, inflammation and stroke. Increased bleeding without reoperation may have limited impact on outcomes, but bleeding that requires reoperation is associated with greater risk.

The available options for intervention have not been prospectively compared in RCTs involving patients with NSTE-ACS. In stabilized NSTE-ACS patients, the guidelines suggest that mode of revascularization should be based on the severity and distribution of coronary artery disease (e.g., as measured by the SYNTAX score [95,96]), as in stable coronary artery disease patients [4]. The benefit from CABG is greatest when performed after several days of medical stabilization [4].

In STEMI, it is recommended that emergency CABG should be considered in cases of unfavorable anatomy for PCI, or PCI failure, but only when a very large myocardial area is at risk and CABG can be completed before necrosis sets in (usually within 3–4 h) [4]. CAGB is therefore very rarely an option in STEMI, even when there are what would normally be regarded as high-risk factors (e.g., left main stem disease). Emergency surgery may also be necessary in cases of mechanical complications of STEMI, such as free left ventricular wall rupture, acute ventricular septal defect or acute mitral regurgitation due to papillary muscle rupture [4]. CABG or further PCI may also be necessary in patients with multivessel disease who have already received PCI on the culprit artery [4]. When this should be performed is the subject of several ongoing studies. A number of factors are associated with higher surgical risk, including older age and comorbidity [4].

Antiplatelet therapy

Guidelines recommend that most patients with ACS receive dual antiplatelet therapy at the time of presentation in order to prevent recurrent ischemic events [4]. However, a significant proportion of ACS patients undergoing angiography require CABG during the index admission (4.0% of STEMI patients and 7.2% of NSTEMI/UA patients in GRACE [90]). Discontinuation of clopidogrel treatment at least 5 days before planned CABG is recommended in order to reduce bleeding-related events [4], although it may increase ischemic events [97]. However, high-risk individuals may require urgent surgery without delay in order to reduce the risk of fatal ischemic events, and predicting which patients will require CABG in the ACS setting is difficult [98]. Furthermore, stopping thienopyridines to allow for surgery puts patients at risk during the interim period.

For patients who have CABG within 5 days of receiving dual antiplatelet therapy, the risk of major bleeding and transfusion can be minimized by applying multiple strategies before and during surgery (e.g., off-pump surgery). If clopidogrel is discontinued prior to CABG, it should be restarted as soon as possible after surgery to decrease the risk of recurrent ACS [4] and to reduce graft occlusion rates. For patients with a recent coronary stent, the decision to continue/discontinue clopidogrel until after surgery will depend on the risk and potential impact of stent thrombosis, and restarting clopidogrel after CABG will depend on whether the stented vessel was revascularized, the type of stent and the time from stent implantation.

Contrary to guidelines, many cardiovascular surgeons will not perform emergency/urgent CABG in patients pretreated with clopidogrel, and education is required to improve adherence to guideline recommendations.

Ticagrelor may be advantageous to cardiovascular surgeons for use in CABG patients if its reversibility data are robust. However, the ONSET-OFFSET study demonstrated that the offset of platelet inhibition after ticagrelor is 3–5 days [12]. There is at least a theoretical possibility that 'free' ticagrelor or active metabolites could decrease the effect of a platelet transfusion.

Conclusion

Guidelines need to be short and practical to aid their implementation. Timing of guideline updates is also an important issue. Frequent updates, as seen in the USA, can be difficult to inculcate into an educationally based practice and to implement generally, but guidelines need to be revised promptly when sets of new important treatments become available. National endorsement and translation (of the pocket version) of ESC guidelines is important to promote local 'ownership' and facilitate implementation. Guidelines should be widely disseminated to national societies, physicians (including primary care), nurses, national regulators, hospital administrators and politicians. In addition, patients and patient associations should have access to the guidelines in order to help drive their local implementation, and healthcare companies also have an interest. Guideline compliance should be routinely audited.

National society congresses are a good forum for dissemination of the guidelines, but small local educational meetings are vital for wider education and adoption of recommendations. Audits to assess adherence to guidelines are also important. Additional tools to facilitate guideline implementation include high-quality educational products such as simple pocket guidelines, slide sets, and physician and patient websites, but these must be produced in a timely manner. Balanced industry support for such initiatives should be welcomed. It would be advantageous for each country to have a national ESC guidelines coordinator

for implementation to work with the medical community and the press.

Expert commentary

This paper is the reflection of a meeting of experts involved in the management of ACS. Much of the discussion focused on new antiplatelet agents and anticoagulants, and the possible impact on future guidelines. Special attention was given to the use of antiplatelet agents in patients undergoing CABG. Methods to improve the usefulness of guidelines in daily practice are proposed. Furthermore, the possible need for national guidelines, which may deviate from those provided by the international societies such as the ESC, was evaluated. The availability of many more potent but more expensive agents on the one hand, and the increasing use of generic agents on the other, will complicate the implementation of the guidelines in many European countries.

Five-year view

Since the early 1980s, we have been witnessing an explosion of research on new anti-thrombotic therapies, resulting in an abundance of new anti-thrombotic agents today. Many new and very promising agents are now available. Both the pharmaceutical industry and academia need to set up studies with the aim of simplifying anti-thrombotic strategies. For reasons of compliance, bleeding risk and cost, it is unrealistic to believe that many patients will be taking three antiplatelet agents, or two antiplatelet agents plus an anticoagulant, for a long period of time, bearing in mind that these patients also have to take lipid-lowering and antihypertensive agents. We have learned from other fields in medicine that too much lowering of blood pressure or glucose levels may be harmful. We must avoid similar outcomes with our new anti-thrombotic strategies in the future. With regard to lipid-lowering treatments, the results of large outcome studies with ezetimibe (in combination with a statin) and with the new cholesteryl ester transfer protein inhibitors, if positive, may significantly change our recommendations in the next 5 years. Similarly, new oral antidiabetic agents with antiatherosclerotic properties (dipeptidyl peptidase inhibitors) may become very important. Whether there will be major improvements in invasive techniques and stent design over the next 5 years is less likely.

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Key issues

- Guidelines are important to facilitate evidence-based medicine, but current guidelines are too complex for the 'average' physician, who requires simple, prescriptive guidance (e.g., treatment algorithms).
- Collaboration between interventional and noninterventional cardiologists, and cardiovascular surgeons can help in developing more balanced guidelines.
- The current definitions for classes of recommendations and the levels of evidence may be interpreted differently, potentially resulting in differences between guidelines in their recommendations, and leading to confusion for guideline users.
- The 'best' evidence (level A or B) comes from randomized controlled trials (RCTs). However, with the exception of 'all-comers RCTs', RCTs often exclude high-risk patients (e.g., elderly patients, patients with Type 2 diabetes and patients with renal impairment, among others), and so do not always reflect 'real life'.
- Registry data indicate that guideline adherence/implementation is poor (although improving), possibly due to their complexity.
- Endorsement of European Society of Cardiology guidelines by national societies is important to facilitate their implementation; however, national guidelines may be deemed necessary in some countries to account for local differences in clinical practice and cost–effectiveness issues. However, national committees and opinion should contribute to European guideline development, and should probably not produce their own guidelines, other than in relation to costs.

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