


Report of the European Society of Cardiology Cardiovascular Round Table regulatory workshop update of the evaluation of new agents for the treatment of acute coronary syndrome: Executive summary

European Heart Journal: Acute Cardiovascular Care
2019, Vol. 8(8) 745–754
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DOI: 10.1177/2048872616649859
journals.sagepub.com/home/acc


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Abstract

Regulatory authorities interpret the results of randomized controlled trials according to published principles. The European Medicines Agency (EMA) is planning a revision of the 2000 and 2003 guidance documents on clinical investigation of new medicinal products for the treatment of acute coronary syndrome (ACS) to achieve consistency with current knowledge

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in the field. This manuscript summarizes the key output from a collaborative workshop, organized by the Cardiovascular Round Table and the European Affairs Committee of the European Society of Cardiology, involving clinicians, academic researchers, trialists, European and US regulators, and pharmaceutical industry researchers. Specific questions in four key areas were selected as priorities for changes in regulatory guidance: patient selection, endpoints, methodologic issues and issues related to the research for novel agents. Patients with ST-segment elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI) should be studied separately for therapies aimed at the specific pathophysiology of either condition, particularly for treatment of the acute phase, but can be studied together for other treatments, especially long-term therapy. Unstable angina patients should be excluded from acute phase ACS trials. In general, cardiovascular death and reinfarction are recommended for primary efficacy endpoints; other endpoints may be considered if specifically relevant for the therapy under study. New agents or interventions should be tested against a background of evidence-based therapy with expanded follow-up for safety assessment. In conclusion, new guidance documents for randomized controlled trials in ACS should consider changes regarding patient and endpoint selection and definitions, and trial designs. Specific requirements for the evaluation of novel pharmacologic therapies need further clarification.

Keywords

Acute coronary syndrome, clinical trials, myocardial infarction, unstable angina, endpoint determination

Date received: 18 April 2016; accepted: 25 April 2016

Introduction

Acute coronary syndrome (ACS) is an active area of drug development. The European Medicines Agency (EMA) released guidance documents for the clinical development of therapies for non-ST-segment elevation myocardial infarction (NSTEMI) in 2000 and ST-segment elevation myocardial infarction (STEMI) in 2003.^{1,2} These documents need updating to achieve consistency with evolving knowledge in ACS.

The Cardiovascular Round Table and European Affairs committee of the European Society of Cardiology convened a dedicated two-day workshop to discuss the revision of the EMA guidance on the clinical investigation of new medicinal products for the treatment of acute coronary syndrome (CPMP/EWP/570/98 and CPMP/EWP/967/01).³ Critical questions relevant to the investigation of new ACS therapies were explored during the workshop. Four topic areas were addressed: (a) patient population and risk stratification; (b) endpoint selection; (c) clinical trial design; (d) research approaches for novel agents. This paper summarizes the key output from the workshop, provides areas of expert consensus, and identifies gaps that need further research.

Patient population

Inclusion of STEMI and NSTEMI patients in clinical trials: together or separate?

Myocardial infarction (MI) is characterized by myocardial cell death resulting from prolonged severe ischaemia.⁴ Patients with STEMI have higher in-hospital mortality rates while NSTEMI patients have higher event rates after discharge,⁵ catching up at one year,⁶ with similar all-cause

death rates after 10 years.⁷ Classification of MI into STEMI and NSTEMI subtypes grossly delineates patients who need immediate reperfusion therapy versus those requiring a less rapid invasive strategy,^{8,9} although this is occasionally challenging. In fact, differentiating STEMI and NSTEMI patients can be complex, and some clinical circumstances may dictate treatment that goes beyond the presumptive diagnosis at presentation (e.g. ongoing ischaemia or extensive necrosis that presents electrocardiographically without ST elevation but evolves as STEMI).

The decision to include both STEMI and NSTEMI patients in a clinical trial or to limit enrolment to one MI type should be based on the specific differences in initial management (Table 1). Including only STEMI patients is reasonable for strategies or techniques for rapid reperfusion or optimization of patency of acute total coronary occlusions (primary percutaneous coronary intervention (PCI) or thrombolysis), adjuvant therapies for reperfusion, or treatments for the prevention of reperfusion damage.^{10,11} Limiting enrolment to NSTEMI patients is reasonable for studies evaluating diagnostic strategies to detect myocardial necrosis or therapies in patients who do not require immediate revascularization.^{12,13} Randomized controlled trials should enrol both STEMI and NSTEMI patients to evaluate common initial therapies such as initial antithrombotic therapy,^{14,15} and therapies targeting the post-acute phase such as anti-ischaemic agents targeting myocardial preservation, anti-remodeling agents aiming to prevent post-MI heart failure,¹⁶ revascularization strategies in partially occluded non-culprit coronary arteries, or therapies aiming to address the residual risk after ACS (e.g. secondary prevention such as lipid-lowering drugs, antithrombotics or lifestyle modifications).^{17,18}

Table 1. Study populations in acute coronary syndrome trials.

Therapy type	STEMI	NSTEMI
Rapid restoration of patency of acute total coronary occlusions	✓	+/-
Thrombolysis	✓	
Adjuvant therapies for reperfusion	✓	
Anti-remodeling agents, prevention of post-MI heart failure	✓	✓
Anti-ischaemic agents, myocardial preservation	✓	✓
New antithrombotic drugs	✓	✓
Diagnostics (biomarkers)		✓
Revascularization strategies	✓	✓
Secondary prevention (e.g. lipid lowering, antithrombotics, anticoagulants)	✓	✓
Lifestyle modifications	✓	✓

MI: myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; STEMI: ST-segment-elevation myocardial infarction.

Although it is recognized that disease classifications cannot capture every clinical scenario, it was recommended to design clinical trials according to these recommendations (Table 2). Deviations from this approach may be appropriate, but they should be justified in the study protocol and discussed with regulatory authorities as needed. When both patient types are included, stratification is recommended to ensure balanced enrolment, but this may not be needed if trials are sufficiently large. Although the presence of ST segment elevation is only one of many important prognostic factors, STEMI and NSTEMI should be studied as subgroups.

Patient risk

The number of events in a clinical trial depends on the trial size and the risk level of the patients. A high risk patient population may be needed to efficiently accrue the target number of events (i.e. by adding ‘enrichment criteria’ to the inclusion criteria),¹⁹ but results may not be applicable to the general population and practising clinicians may have difficulty translating the results into their daily practice. On the other hand, a broader (i.e. lower risk) patient group may be selected with a lower event rate, requiring a larger number of patients and/or an event-driven study design. No clear recommendation could be agreed for this decision. Ultimately, balance must be achieved between enrolling the correct broad target population in confirmatory trials (i.e. with representation of the elderly, women, ethnic subgroups and patients with comorbidities), while also ensuring that sufficient homogeneity is maintained to avoid diluting the effect size.

Inclusion of unstable angina: is it still appropriate?

The proportion of ACS patients with unstable angina (UA) (i.e. myocardial ischaemia at rest or minimal exertion in the absence of cardiomyocyte necrosis)⁹ is estimated at

20–30% of ACS admissions,^{20–22} although the proportion is decreasing with high-sensitivity troponin assays.^{4,23,24} Many of the patients previously included in trials as ‘unstable angina’ would now be classified as NSTEMI using high-sensitivity troponin assays. This reclassification raises the question of whether the diagnosis of UA should be reconsidered.²⁵ For this reason, the current diagnosis of UA has been questioned.²⁵ However, excluding patients with UA from ACS trials can be operationally challenging. Although excluding UA might strengthen the treatment-effect signal and reduce the number of patients needed in a clinical trial, this may result in slower recruitment. Another challenge relates to the time of randomization, since treatment or enrolment decisions may need to be made before biomarker results are available. Thus, UA cannot always be excluded in very early treatment trials, since a definite diagnosis may not yet be available. On the other hand, although patients with UA are at lower mortality risk than patients with NSTEMI^{26,27} even though they are managed more conservatively,²⁸ research focused on patients with UA is still needed to characterize the pathophysiology and, particularly, disease progression, and to identify therapies that might be specifically effective in these patients. Despite these controversies, the exclusion of UA patients from most ACS trials seems, in general, appropriate if such decisions can be based on high sensitivity troponin assays.

Utility of ACS risk stratification in randomized control trials

International ACS guidelines recommend the use of risk scores such as the Global Registry of Acute Coronary Events (GRACE)²⁹ or Thrombolysis in Myocardial Infarction (TIMI)³⁰ in the clinical care of patients with ACS.^{8,9,31} These (and other)³² scores can be used to predict the risk of death, death or MI, and stroke or major bleeds,³³ and they are useful to guide early treatment decisions.³³ Also, scores to assess risk after the early phase may be useful to select patients for trials assessing different strategies for secondary prevention therapies.³⁴

Risk scores are inconsistently implemented in global clinical practice.³⁵ One of the reasons might be that the impact of using those risk scores on patient outcomes has never been studied. In addition, clinicians may be reluctant to use these scores because of their perceived complexity although risk score calculators could easily be integrated into electronic health records. Uncertainty about which of the several available scores is most appropriate in a given setting may also contribute to the lack of their widespread adoption in clinical practice. Agreement on a single risk score might result in better penetration. The GRACE score is applicable to all ACS patients since it was derived from a large population of unselected ACS patients, has been externally validated, and predicts short-term and five-year morbidity and mortality.³⁶ By contrast, the TIMI risk score was derived from a selected population enrolled in a randomized

Table 2. Key recommendations.

Topic	Recommendation
Inclusion of STEMI and NSTEMI patients in clinical trials: together or separate?	<ul style="list-style-type: none"> • Including only STEMI patients is reasonable for strategies or techniques for rapid reperfusion or optimization of patency of acute total coronary occlusions (primary PCI or thrombolysis), adjuvant therapies for reperfusion, or treatments for the prevention of reperfusion damage. • Limiting enrolment to NSTEMI patients is reasonable for studies evaluating diagnostic strategies to detect myocardial necrosis or therapies in patients who do not require immediate revascularization. • Randomized controlled trials should enrol both STEMI and NSTEMI patients to evaluate common initial therapies such as initial antithrombotic therapy, and therapies targeting the post-acute phase such as anti-ischaemic agents targeting myocardial preservation, anti-remodeling agents aiming to prevent post-MI heart failure, revascularization strategies in partially occluded non-culprit coronary arteries, or therapies aiming to address the residual risk after ACS (e.g. secondary prevention such as lipid lowering, antithrombotics, anticoagulants, or lifestyle modifications).
Should unstable angina patients be included in ACS trials?	<ul style="list-style-type: none"> • The exclusion of UA patients from most ACS trials seems, in general, appropriate if such decisions can be based on high sensitivity troponin assays • Unstable angina patients can be enrolled in ACS trials when at the time of randomization the diagnosis of NSTEMI may not be known but, for these trials, pre-specified subgroup analyses of NSTEMI and unstable angina should be planned (and attempts made to adequately power to the extent possible).
How should ACS risk stratification be used in randomized, controlled trials?	<ul style="list-style-type: none"> • Primary analyses should be done in the total population • Secondary analyses should be done by risk scores, using validated risk scores for the early (e.g. GRACE, TIMI) or later phases • At a minimum, risk score data should be provided to regulators in the submitted clinical file • Limitations should be recognised and described in publications; even pre-specified subgroup analyses are often underpowered
Which are the appropriate efficacy and safety endpoints for ACS randomized controlled trials?	<ul style="list-style-type: none"> • CV death + MI for most studies • Some studies might also include ischaemic stroke, depending on the drug and/or population • Endpoints that depend on physician preferences or local practices are not recommended (e.g. ischaemia-driven revascularization procedures) • The clinical setting is key to determining the appropriateness of additional composite endpoints • A well thought-out justification supporting the composites chosen could be provided to regulators during the study planning before the protocol is finalized • Need consistent reporting of bleeding. Recommendation to report bleeding by TIMI, BARC and ISTH for future trials.
Background therapy and appropriate comparator arm	<ul style="list-style-type: none"> • Background therapy should relate to the disease state being studied. For example if the endpoint is CV death and MI, then background therapy should reflect the usual regimen known to influence this endpoint (i.e. lipid lowering therapy, aspirin, beta-blockers, ACE-inhibitor) • Any potential difference in background therapy should be balanced by randomization. If it is not, then stratified randomization or stratified analysis should be applied.
Trial duration	<ul style="list-style-type: none"> • Thirty day follow-up is probably adequate for acute phase treatments for ACS, whereas a minimum of one-year follow-up or possibly longer is needed for treatments continued after discharge from hospital. Event driven designs may be considered for secondary prevention treatments.

ACE: angiotensin converting enzyme; ACS: acute coronary syndrome; BARC: Bleeding Academic Research Consortium; CV: cardiovascular; GRACE: Global Registry of Acute Coronary Events; ISTH: International Society of Thrombosis and Haemostasis; MI: myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment-elevation myocardial infarction; TIMI: thrombolysis in myocardial infarction; UA: unstable angina.

trial to predict a 'softer' composite outcome, and it has been less well validated.³⁶

In clinical trials, demonstrating a treatment effect depends critically on the underlying risk. Several important factors

(e.g. age, gender, renal insufficiency, frailty, prior cardiovascular events) identify patients at risk for both adverse outcomes from thrombotic events, as well as increased bleeding risk. Selecting high-risk patients not only influences the

treatment effect but may increase the risk of adverse events, such as bleeding with anti-thrombotic agents. Rather than enrichment strategies, risk scores can be applied across a broader group of patients to identify signals of differential treatment (or safety) responses across risk subgroups. From a regulatory perspective, risk scores should be reported or adequate data should be provided in the study files to enable risk score(s) calculations. Risk-based analyses can contribute to the interpretation of study results and provide information about generalizability to the wider population of unselected ACS patients, especially in highly heterogeneous populations.

Primary analyses should be performed in the overall population to maintain the rigour and statistical validity of the clinical trial. Analyses by validated and accepted risk scores and key subgroups should be included as secondary or supportive evaluations. The limitations of risk-based subgroup analyses should be described when reporting trial results. These analyses may lead to further prospective studies or post-marketing surveillance priorities in specific, targeted populations. Targeted, 'precision' medicine is an area of interest and has the promise of improving patient care by identifying patients who are most likely to benefit from a specific treatment. This approach may also be the most cost-effective. Risk scores and other data (e.g. genetic markers) may be useful to identify responders and non-responders, but additional randomized trials would still be needed to test interventions within these targeted populations.

Endpoints

Efficacy endpoints

The primary composite efficacy endpoints used in ACS trials typically include a composite of death (all-cause or cardiovascular), non-fatal reinfarction and non-fatal stroke. Some composites also include revascularization, cardiogenic shock or heart failure. Endpoints such as stent thrombosis, or left ventricular remodeling, might be of particular interest for therapies targeting the initial myocardial injury.

The use of cardiovascular death instead of all-cause death in the primary composite endpoint avoids the dilution of a potential beneficial treatment effect, while the use of all-cause death is recommended as a safety measure.³⁷ Accordingly, if the cardiovascular death component of the composite endpoint is significantly reduced but the point estimate for all-cause death is shifted towards the null, this may indicate an increase in non-cardiovascular mortality. The Supplementary Material, Table 1, displays examples where cause-specific death was reduced but all-cause death was not, which emphasizes the importance of performing detailed analyses of both cause-specific and all-cause endpoints. All-cause mortality will always be evaluated by regulators for safety, even if it is not the primary endpoint of the trial.

MI definitions also vary across studies. Troponin elevation is now essential in MI diagnosis, although concerns have been raised about a lack of biological equivalence between different manufactured assays³⁸ given the many factors that can influence the 99th percentile upper reference limit within the reference population, which may have a potential impact on MI endpoints.⁴ Troponin release occurs in other clinical conditions associated with myocardial injury induced by mechanisms other than coronary obstruction. Although the definition of type 2 MI is controversial³⁹ and may be modified in the ongoing updating of the universal definition of MI, it was recommended to classify MIs according to the defined MI subtypes to delineate spontaneous MIs from MIs unlikely to be influenced by treatment (e.g. type 2, secondary to imbalance between myocardial oxygen supply and demand) or MIs that are generally viewed as less severe or with a better prognosis (e.g. type 4a, related to PCI).⁴ To establish consistency, the group agreed that future trials should define MI according to the third universal definition to facilitate interpretation of data across clinical trials. This approach is considered more transparent and should enhance the interpretability of results.

In patients where reinfarction is suspected from clinical signs or symptoms following the initial MI, an immediate measurement of cardiac troponin is recommended. A second sample should be obtained 3–6 h later. If the first cardiac troponin concentration is elevated but stable or decreasing at the time of suspected reinfarction, the diagnosis of reinfarction requires a 20% or greater increase of the cardiac troponin value in the second sample. If the initial cardiac troponin concentration is normal, the criteria for new acute MI apply.⁴

Stroke accounts for the smallest proportion of events in ACS trials. A majority of participants agreed that stroke should be included in the composite endpoint only if there is a biological rationale suggesting a treatment effect or a possible treatment hazard impacting on stroke risk. Otherwise, including ischaemic stroke as part of the composite endpoint may add complexity and noise rather than clarity. Haemorrhagic strokes (or all-cause stroke when the type is uncertain or the intervention has the potential to increase the risk of any type of stroke) should be assessed as a safety outcome.

Revascularization endpoints are sometimes incorporated in composite endpoints. Revascularization endpoints in a composite may be clinically relevant, but they are subjective and not always biologically driven and hence may add 'noise' to the primary endpoint. For example, the need for urgent revascularization can reflect investigator preference or local practice, rather than the effect of a study drug. Moreover, independent adjudication of these endpoints is necessary but can be challenging depending on the information and documentation available to the adjudication committee. Target lesion or target vessel revascularization endpoints can also be used as part of a composite endpoint,

but pre-specified criteria need to be documented (e.g. target lesion failure (TLF) defined as composite of cardiac death, myocardial infarction attributable to target vessel (TV-MI), or ischaemic-driven target lesion revascularization (ID-TLR), luminal measurements, presence of symptoms, evidence and degree of urgency) are needed to identify and adjudicate these events. Similarly, angina needing revascularization requires a robust pre-specified definition (e.g. based on ischaemic pain, urgent/emergency hospitalization, electrocardiogram (ECG) and/or imaging data), adjudication, and a double-blind design or assessment without knowledge of the treatment group to minimize the introduction of bias into clinical decision making, to be accepted as a valid component of a composite endpoint. Inclusion of revascularization endpoints in a composite endpoint might be most suitable for strategy or intervention trials where the primary goal of therapy is revascularization or testing a new coronary stent (e.g. drug-eluting-bioresorbable stents), in contrast to drug studies where the goal of therapy may differ. Ischaemia requiring urgent revascularization could appropriately be included in a composite endpoint where there is a biological rationale for a drug to impact the pathophysiology underlying the need for urgent revascularization, provided a clear and tight definition is given.

Interest in stent thrombosis as an endpoint emerged with the advent of drug eluting stents. However, stent thrombosis can only be viewed as a surrogate endpoint for a clinical event when its occurrence would be clearly related to measurable clinical outcome (e.g. MI or sudden death); otherwise the relevance of stent thrombosis is uncertain. Stent thrombosis occurs infrequently, is of less concern with newer technologies, and generally should not be a component of the primary efficacy endpoint. However, it may be a reasonable secondary endpoint for interventional device trials or trials of antithrombotic drugs during or after PCI.

Each component of a composite endpoint should be individually reported. The point estimate for all components should be directionally similar, even if the effect in the individual components is not statistically significant. When consistency across components is not observed (i.e. two or more components have point estimates that move in different directions), the interpretation of the overall composite is complex and regulatory agencies may require additional analyses and/or specific wording in the label to reflect the results.

Although net clinical benefit endpoints (i.e. the combination of efficacy and safety in trials of antithrombotics) can be informative, the interpretation of a net clinical benefit endpoint is complex because the elements are necessarily of different severity. The potential for one component to overshadow other components is a limitation of their use. Therefore, it is generally appropriate to report efficacy endpoints (e.g. ischaemic events) and safety endpoints (e.g. bleeding events) separately, and to pre-specify definitions in the protocol (e.g. allocation of an initial ischaemic stroke that becomes haemorrhagic) in order to interpret the

net clinical benefit. Since many ACS drugs target thrombosis, the risk for bleeding (safety) correlates closely with the risk for cardiovascular death or MI (efficacy). Therefore, additional work that differentiates safety and efficacy is encouraged.

Achieving general consistency in endpoint selection is important, but endpoints may need to be tailored according to their relevance for specific patient types (e.g. STEMI versus NSTEMI) or therapies (e.g. acute versus chronic, proven antithrombotic drugs versus novel biologic agents, drugs to reduce ischaemia versus drugs to prevent heart failure). As a minimum, most ACS trials should include the composite of cardiovascular death and non-fatal MI in the primary efficacy endpoint.

Safety endpoints

Bleeding is the predominant safety concern in most recent ACS trials, although emerging therapies may have different safety profiles that raise unique issues in the future. Several different bleeding definitions have been used in clinical trials, and this heterogeneity impairs the interpretation of safety, especially across trials. The need to adopt standard definitions for bleeding events has been recognised.^{37,40} The Bleeding Academic Research Consortium (BARC) undertook an initiative to standardize reporting⁴⁰ but consensus has not yet been reached on a single reporting approach. Trials that potentially impact on bleeding should report bleeding events such that BARC, TIMI or International Society of Thrombosis and Haemostasis (ISTH)⁴¹ criteria can be applied, even if the trial has chosen a different bleeding composite. Combined use of BARC, TIMI or ISTH definitions could be considered for future randomized controlled trials and/or regulatory submissions. Trial specific bleeding definitions should be avoided.

Considerations for randomized controlled trial designs

Background therapy

In general, regulators expect that the background therapy should reflect the current standard of care recommended by international guidelines.^{8,9} However, the availability of guideline recommended treatments depends on external factors such as time delays in the uptake of new ACS therapies,⁴² differences in local clinical practice, local reimbursement policies and accessibility of specific therapies. Thus, variations in treatment strategies exist even within the context of international guideline recommendations.

Estimating event rates and powering trials appropriately can be problematic because the ACS field is rapidly evolving and the standard of care frequently changes. Of the background treatments for ACS, revascularization may

have a major impact on later events. Therefore, imbalances in the use of revascularization between arms, or underutilization of revascularization may confound interpretation of study results. Regional differences in revascularization practices can be problematic in multi-regional trials. Additionally, some background therapies can affect adverse event risk, especially bleeding risk (e.g. aspirin dose, anti-coagulants, thrombolytics, antiplatelets). The extent to which background therapy should be specifically standardized in terms of interventions, timing, drugs and dosing will depend on the study drug's mechanism of action or the specific question being addressed by the trial. Regulators generally require background therapy that is based on the available evidence for accurate assessment of benefits and risks of the therapy being tested and relevant to the majority of the population under study.

Comparator arm

Randomized controlled trials are designed to determine the efficacy and safety of a new treatment compared to either placebo on top of standard care, an active comparator, or a strategy of withdrawing other active therapy. When designing a trial, selection of an appropriate comparator is critical but sometimes challenging. The comparator should be clinically relevant and correspond to current medical practice with an adequate evidence base. In some circumstances, however, the standard of care has been adopted but never formally studied in a randomized controlled trial. In general, treatments considered to be standard of care should be part of the background therapy, although flexibility should be allowed if adding the investigational agent to background therapy might be expected to increase the risk of adverse events (e.g. addition of new antithrombotic therapies to background standard of care with dual antiplatelet therapy). The use of superiority and non-inferiority design trials is an important methodological issue,⁴³ but was not a topic of discussion at the meeting.

Trial duration

The optimal duration of a trial depends on the treatment objective. Follow-up beyond the end of therapy in the study is desirable, but the ideal length depends on the mechanism of action, pharmacokinetics of the drug, and the duration of treatment. A therapy given for a very short duration in the acute setting would be expected to impact short-term events rather than influencing survival over the longer term (e.g. ≥ 1 year), although a sustained long-term survival benefit with reperfusion therapy has been demonstrated.⁴⁴ Thirty-day follow-up is probably adequate for acute phase treatments for ACS, whereas a minimum of one-year follow-up or possibly longer is needed for treatments continued after discharge from hospital. Event-driven designs may be considered for secondary prevention treatments.

From an operational and feasibility standpoint, long follow-up is costly and may introduce analytic challenges because of those lost to follow-up, trial fatigue, events unrelated to the study drug or bias introduced by un-blinding or the influence of early events on management in the control arm. However, several healthcare systems now have robust methods of long-term mortality (and some have morbidity) reporting based on routine data and this approach has been validated and demonstrated to be feasible and much less costly than long-term conventional follow-up.⁴⁵⁻⁴⁷

Evaluation of novel therapies

Many novel therapies for ACS treatment in the acute phase and secondary prevention are on the horizon, including antibodies and other protein-based therapies, cell therapy, gene therapy and RNA-based therapies.⁴⁸⁻⁵⁴ A comprehensive review of these therapies is outside the scope of this manuscript, but it is useful to consider in general how development pathways might need to be modified to accommodate their unique characteristics.

Several challenges for the clinical and regulatory evaluation of new therapies were identified, including (a) the opposing forces between the lack of feasibility to enrol thousands of patients in randomized controlled trials with such therapies against the inability to assess its effects on traditional primary endpoints with smaller trials; (b) the issue of bias due to blinding limitations and ethical implications and effects of sham procedures; (c) the ignorance of the most appropriate endpoint to evaluate these interventions; (d) the unclear role of the use of surrogate endpoints (e.g. infarct size, global or regional left ventricular function) given the inconsistencies found between trials with surrogate endpoints and adequately powered randomized controlled trials;^{48,49,55-58} and (e) the long-term safety of novel therapies, particularly biological therapies, such as cell or gene therapies or some monoclonal antibodies, is a new need that needs to be addressed specifically and will require special approaches, such as very long follow-up or specific surveillance policies. Further discussion to address these challenges from a regulatory point of view is needed.

Conclusion

Development programs of new treatments for ACS should consider the changes that have occurred in ACS definitions, epidemiology, standards of care and clinical outcomes. Clinical investigators, trialists and pharmaceutical companies should also consider this evolution and update relevant aspects of patient selection, study design and endpoints in the context of ACS pathophysiology and the agent's expected mechanism of action for future studies evaluating new drugs for the treatment of ACS, or for reducing events after ACS. The evaluation of novel therapies may require different and more flexible trial designs, more cost-effective

recruitment and follow-up, new endpoints and a special emphasis on long-term safety.

Acknowledgements

This paper was generated from discussions during a Cardiovascular Round Table (CRT) Workshop organized on 30–31 March 2015 by the European Society of Cardiology (ESC). The CRT is a strategic forum for high-level dialogues between industry and ESC leadership to identify and discuss key strategic issues for the future of cardiovascular health in Europe. The opinions presented in this manuscript represent those of the individual participants and not of their institutions. The authors acknowledge the contributions of Emilie Niedercorn and Mathieu Weitbruch for their contributions and participation during the meeting, and Florence Bakry of the ESC for her organization and contributions to the planning of the workshop.

Conflict of interest

Hector Bueno: research grants from AstraZeneca and advisory/speaker fees from Abbott, AstraZeneca, Bayer, BMS, Daiichi Sankyo, Eli Lilly, Ferrer, Menarini, Novartis, Pfizer, Sanofi and Servier; Isabelle Richard-Lordereau: employee of Bristol-Myers Squibb; Keith AA Fox: research grants from Bayer/Janssen, Lilly, AstraZeneca, GSK; personal fees from Bayer/Janssen, Sanofi/Regeneron, AstraZeneca; Carola P. Friedman: employee of Novartis; Christophe Gaudin: employee of Sanofi, stock ownership in Sanofi; Samantha Goldman: employee of Daiichi Sankyo; Melanie Hemmrich: employee of Bayer; Robert Henderson: honoraria from Quantum Imaging; Anders Himmelmann: employee of AstraZeneca; Alar Irs: Employee of the Estonian Agency of Medicines and member of the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP); Neville Jackson: employee of Pfizer; Stefan K. James: institutional grants and honoraria from AstraZeneca, The Medicines Company and Bayer; Hugo A. Katus: honoraria for lectures from AstraZeneca, Bayer Health, Roche Diagnostics; research grants from AstraZeneca, Bayer Health; Ian Laws: employee of GSK; Roxana Mehran: Research grants from Eli Lilly, AstraZeneca, The Medicines Company, BMS/Sanofi-Aventis; Consulting fees from AstraZeneca, Bayer, CSL Behring, Janssen Pharmaceuticals, Merck & Company, Osprey Medical, Watermark Research Partners; Scientific Advisory Board for Abbott Laboratories, Boston Scientific, Covidien, Janssen Pharmaceuticals, The Medicines Company, Sanofi-Aventis Scientific Advisory Board; Seleen Ong: employee of Pfizer; Marco Roffi: institutional research grants from Abbott Vascular, Biotronik, Biosensor, Medtronic, Boston Scientific; Martin Rose: employee of the US Food and Drug Administration; Peter R. Sinnaeve: Institutional fees from Astra Zeneca, Boehringer, Sankyo, BMS, Pfizer, Sanofi; grant from AstraZeneca; Wendy Gattis Stough: consultant to European Drug Development Hub, Relypsa, CHU Nancy, European Society of Cardiology, Heart Failure Association of the European Society of Cardiology, Heart Failure Society of America, Overcome, Stealth BioTherapeutics, Covis Pharmaceuticals, University of Gottingen and University of North Carolina; Frans Van de Werf: Institutional grants from Boehringer Ingelheim, Merck, The Medicines Company and Sanofi; honoraria for lectures and consultancy from Boehringer-Ingelheim, Astra Zeneca, Merck, Roche; Claire Varin: employee

of Servier Freek W. A. Verheugt: honoraria for speaker fees and consultancy honoraria from AstraZeneca, Medtronic, Bayer Healthcare, Boehringer-Ingelheim, BMS/Pfizer and Daiichi-Sankyo; Mathieu Weitbruch: Employee of Novartis

The following individuals declare that they have nothing to disclose: Pieter de Graeff; Joseph Emmerich; Amany El-Gazayerly; Andrea Laslop; Krishna Prasad; Giuseppe Rosano; Kristian Thygesen; Maria de los Angeles Alonso García.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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