

Representativeness in randomised clinical trials supporting acute coronary syndrome guidelines

Caterina Mas-Llado^{1,2,3}, MD; Maribel González-Del-Hoyo^{2,4}, MD, PhD; Joan Siquier-Padilla⁴, MD; Laura Blaya-Peña⁴, MD; JJ Coughlan^{5,6}, MB BCh, MD; Bernardo García de la Villa^{1,2}, MD; Vicente Peral^{2,3,4}, MD, PhD; Xavier Rossello^{2,3,4,7}, MD, PhD

¹ Cardiology Department, Hospital de Manacor, Manacor, Spain

² Health Research Institute of the Balearic Islands (IdISBa), Palma, Spain

³ Facultat de Medicina, Universitat de les Illes Balears (UIB), Palma, Spain

⁴ Cardiology Department, Hospital Universitari Son Espases, Palma, Spain

⁵ Deutsches Herzzentrum München und Technische Universität München, Munich, Germany

⁶ Cardiovascular Research Institute, Mater Private Network, Dublin, Ireland

⁷ Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain

Address for correspondence:

Xavier Rossello, Cardiology Department, Hospital Universitari Son Espases, Health Research Institute of the Balearic Islands (IdISBa), Palma de Mallorca, Spain.

Phone number: +34 871 20 50 50 (ext. 64527)

Email: fjrossello@ssib.es

ABSTRACT

Aims. Clinical practice guidelines (CPGs) are published to guide the management of acute coronary syndrome (ACS). We aimed to critically appraise the representativeness and standard of care of randomised clinical trials (RCTs) supporting CPGs for ACS.

Methods and Results. American and European CPGs for ST- and non-ST-elevation ACS were screened to extract all references (n=2128) and recommendations (n=600). Among the 407 primary publications of RCTs (19.1%), there were 52.6% and 73.2% recruiting patients in North America and Europe, respectively, whereas other regions were largely underrepresented (e.g., 25.3% RCTs recruited in Asia). There was 68.6% RCTs enrolling patient with ACS, whereas the remaining 31.4% did not enroll any patient with ACS. There was underrepresentation of some important subgroups, including elderly, female (29.9%) and non-white patients (<20%). The incidence and type of reperfusion reported in these RCTs were not reflective of current clinical practice (the percentage of patients who underwent percutaneous coronary intervention (PCI) among all RCTs was 42.7%; whereas for ST-Elevation Myocardial Infarction patients, the number of participants who underwent fibrinolysis was 3.3-fold higher than those who underwent primary PCI). All-cause mortality in these RCTs was 11.9% in RCTs with a follow-up ≤ 1 year.

Conclusion. RCTs supporting CPGs for ACS are not fully representative of the diversity of the ACS population and their current standard of care. While some of these issues with representativeness may be explained by how evidence has been accrued over time, efforts should be made by trialists to ensure that the evidence supporting CPGs is representative of the wider ACS population.

KEYWORDS

Acute coronary syndrome; Cardiovascular disease; Clinical Practice Guidelines; Evidence-based medicine; Randomised Clinical Trials.

INTRODUCTION

Clinical practice guidelines (CPGs) are published to guide the diagnosis, treatment and prevention of acute coronary syndrome (ACS). They aim to inform clinical decision making by providing a set of evidence-based recommendations. Under this framework, these recommendations are classified according to their strength (class of recommendation), and the underpinning level of evidence (LOE).¹ Randomized clinical trials (RCTs) are a key paradigm in evidence-based medicine,² and are key to understanding the recommendations provided by CPGs.

Representativeness means that a subset of a population accurately reflects the characteristics of the larger group. Adequate representativeness of the patients enrolled in RCTs is critical for the generalizability of their findings.^{3,4} Before the inclusion of participants from other regions of the world became a standard in global trials, the majority of RCTs were conducted in Western Europe and Northern America.⁵ Previous studies have consistently shown that some subgroups of patients (i.e. women, older people, and non-white ethnic groups) have been historically underrepresented in ACS RCTs, despite the fact that they comprise a substantial proportion of patients with ACS.⁶

Recent advances in the pharmacological and invasive management of patients with ACS have led to significant improvements in prognosis, and have consequently changed the proportion and characteristics of ACS survivors.⁷ Therefore, the recommendations made by contemporary CPGs may be based on RCTs tested predominantly in certain geographic regions, with a preponderance of young, white, male patients, and may not be reflective of the current standard of care.^{4,8,9} A thorough evaluation of the RCT based evidence which supports ACS guidelines may be useful to identify if this is the case.

The American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) have published CPGs to guide the management of both ST-Elevation Myocardial Infarction (STEMI), and Non-ST-Elevation Acute Coronary Syndrome

(NSTEMI-ACS).¹⁰⁻¹³ Previous reports appraising CPGs content have mainly focused on tabulating the number of recommendations according to their class and LOE,^{14,15} or evaluating the LOE based on the type of funding¹⁶ or the type of management (e.g., recommendations regarding therapeutic or diagnostic approaches).¹⁷

A better understanding of the underlying study population and the standard of care at the time RCTs were conducted may be useful to evaluate the representativeness of the evidence supporting American and European CPGs. Using a systematic approach, we have evaluated all RCTs cited in ACC/AHA and ESC ACS CPGs, with the following aims: (1) to quantify geographic imbalances in RCTs recruitment; (2) to determine the type of patients recruited (ACS vs non-ACS and STEMI vs. NSTEMI-ACS); (3) to report baseline characteristics and major exclusion criteria; (4) to determine the prevalence of the invasive and reperfusion approaches; and (5) to describe the relevant clinical outcomes. The overarching aim of this analysis is to provide a critical appraisal of the representativeness of the evidence supporting current ACS guideline recommendations.

METHODS

Clinical practice guidelines

Current ESC and ACC/AHA CPGs for ACS were identified as those posted on the ESC (<https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines>) and ACC (<https://www.acc.org/guidelines>) websites as of January 1, 2022. Only guideline documents that included recommendations organized by class and LOE, clearly highlighted and separated from the rest of the text, were included for this analysis. Focused updates were not included because they are not representative of the evidence base for an entire topic.¹⁸ Four documents were eligible: (a) 2013 ACC/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, (b) 2014 ACC/AHA Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndrome, (c) 2017 ESC Guidelines for the management of acute

myocardial infarction in patients presenting with ST-segment elevation, and (d) 2020 ESC Guidelines for the management of acute coronary syndrome in patients presenting without persistent ST-segment elevation.^{10–13}

References supporting CPGs

All references were retrieved from the four guidelines (**Figure 1**). Two authors (JS-P and LB-P) screened each title and abstract independently and classified each reference according to whether they contained randomized data or not. Further, RCTs were classified into two types: primary publications of RCTs, and secondary publications of RCTs (e.g., secondary endpoints, subgroup analyses, post hoc analyses). To avoid overrepresenting some trial populations, secondary analyses of RCTs were excluded from our analysis. Any disagreements between the two authors over the classification of a paper were resolved after consultation with a third researcher (XR).

Randomised clinical trials

After screening of all references and the selection of references reporting on the primary publications of RCTs, the information relevant to representativeness from each RCT was extracted by one of the authors (CM-L).

Information included in this analysis was collected at two levels. Some information was collected at the RCT-level (e.g., whether a RCT was recruiting patients in Europe), whereas other data was collected at the aggregated-patient level (e.g., the number of women recruited in each RCT). This latter approach was useful to provide more accurate percentages (e.g., the number of women provided in each RCT was added up and then divided by the total number of participants in all RCTs). Of note, aggregated data was collected only for the control group under the hypothesis that it was the arm that better represented the standard of care at the time the RCT was conducted (e.g., the number of patients who underwent fibrinolysis or primary percutaneous coronary intervention in each control group were gathered from all RCTs). For head-to-head trials with active comparators (e.g., primary percutaneous coronary

intervention vs fibrinolysis), the type of reperfusion was not taken into account when calculating percentages, because 100% of the control group had received one of the approaches by definition.

Recommendations

Recommendations were identified as clearly displayed statements highlighted and separated from the rest of the document text, with each recommendation having both a class of recommendation and LOE.¹⁸ Recommendations were extracted from each of the CPGs by a single reviewer (XR) and validated by another reviewer (MG-D-H). The references used to support each recommendation were also retrieved and linked with the produced dataset.

Recommendations were categorized according to their class and LOE. Based on their class, recommendations can be categorized as: I for those with evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective; II for those with conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure; and III for those with evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful. Class II is subsequently sub-categorised as IIa if the weight of evidence/opinion is in favour of usefulness/efficacy, or IIb if usefulness/efficacy is less well established by evidence/opinion. In this analysis, we evaluated all class II recommendations together.^{12,13}

According to the LOE, recommendations can be categorized as LOE A if they are supported by multiple RCTs or meta-analyses, LOE B if they are supported by data derived from a single RCT or large non-randomised studies, and LOE C if the recommendation is based on consensus of opinion of the experts and/or small studies, retrospective studies, registries.^{12,13}

Data analysis

Analyses were made at several levels. At the reference-level, we calculated the percentages of RCT references included in the guidelines (as a percentage of the total number of references). At the RCT-level, we calculated percentages by type of recommendation (class and LOE), and by guidelines (ESC vs ACC/AHA for geographic comparisons; or STEMI vs NSTEMI vs ACS for comparisons of type of ACS). These comparisons were made using either the χ^2 test, or a nonparametric test for trend across ordered groups (e.g., LOE A vs. B vs. C). At the aggregated patient-level, we provided either absolute figures (e.g., the number of patients recruited in the control and the active arm), or provided percentages obtained by adding all the information collected in the control group of each RCT (e.g., 396 trials provided the number of female patients, so the numbers in the control groups were added up and used to calculate the percentage of female patients in all control groups in the 396 trials). For the baseline characteristics, categorical data were presented using frequencies and percentages, whereas continuous data were presented as means and standard deviations (SD). All statistical analyses were performed using STATA software, version 15.1 (Stata Corp, College Station, Texas, USA).

RESULTS

General description of references, RCTs and recommendations in ACS guidelines

We extracted 2128 non-duplicated references with PMIDs (PubMed Identifier) across the four guidelines (**Figure 1**). Among these extracted references, 407 (19.1%) were primary publications of RCTs. There were also 151 (7.1%) secondary publications of RCTs, which were not included. The majority of included RCTs (75.7%) were published after the year 2000.

The percentage of RCTs cited in each guideline was 21.8% in the ACC/AHA STEMI guideline, 30.1% in the ESC STEMI guideline, 17.0% in the ACC/AHA NSTEMI-ACS guideline and 21.5% in the ESC NSTEMI-ACS guideline (**Figure 1**). Of the 407 cited RCTs, 305 (74.9%) were only

cited in one CPG, with the remaining 102 cited in more than one CPG (19.7%, 3.9%, and 1.5% in 2, 3 and 4 CPGs, respectively).

There were 600 recommendations between the 4 CPGs (123 in ACC/AHA STEMI, 160 in ESC STEMI, 185 in ACC/AHA NSTEMI-ACS, and 132 in ESC NSTEMI-ACS). Primary publications of RCTs were cited 487 times in these recommendations. Among them, 245 (52.5%) were cited once, whereas 242 were cited in at least two recommendations (within, or between guidelines).

Geographic representativeness

Most of the included RCTs recruited patients from North America and Europe (52.6% and 73.2% respectively), with substantial differences between American and European guidelines (**Figure 2 A**). Other regions were largely underrepresented in the RCTs used to support the CPGs, with only 25.3% of recruited patients being from Asia, 20.4% from Latin-America, 19.9% from Australia, and 12.8% from Africa (12.8%) (**Figure 2 A**).

To investigate whether certain recommendations were more European- or American-centric, the percentage of RCTs recruiting patients from North America and Europe are also reported by type of recommendation (class and LOE) in **Figure 2 (panels B-E)**. In the ESC guidelines, the percentage of RCTs recruiting patients in North-America was higher for class I than for class II or III recommendations ($p=0.004$). Similarly, LOE A recommendations had an almost significantly higher percentage of RCTs recruiting European participants than LOEs B and C ($p=0.058$). In ACC/AHA guidelines, there were non-significant differences in the percentage of RCTs recruiting in North America and Europe by LOE.

Primary diagnosis of the study population

There were 279 (68.6%) RCTs enrolling patients with ACS, with some heterogeneity across guidelines (**Figure 1** shows differences by guideline). The remaining 128 (31.4%) RCTs

enrolled patients with other conditions, with 80 RCTs (19.7%) specifically excluding patients with ACS according to their inclusion criteria.

The percentage of RCTs enrolling patients with STEMI in the STEMI guidelines (both ESC and AHA) was significantly different by classes of recommendations (I, 67%; II, 78%; III, 80%; $p=0.028$), but not across LOEs (A, 75%; B, 70%, C 64%; $p=0.246$) (**Figure 3 A**). For NSTEMI-ACS guidelines, there were no significant differences in the distribution of RCTs recruiting patients with NSTEMI-ACS, but percentages ranged between 55% and 36% (i.e., in most RCTs supporting evidence in NSTEMI-ACS guidelines, the majority of RCTs did not recruit patients with NSTEMI-ACS) (**Figure 3 B**).

A total of 1,582,039 patients were recruited in the 407 RCTs (728,605 in the control arm, and 853,434 in the active arm). We quantified the number and type of ACS patients recruited in the control group of each RCT and pooled this information together. Amongst the patients in the control arms, 35.2% had STEMI and 22.3% had NSTEMI-ACS. The percentages of patients with STEMI in STEMI guidelines, and with NSTEMI-ACS in NSTEMI-ACS guidelines, are reported by type of recommendation in **Figure 3 (panels C-D)**. Of note, there were 55 RCTs including both STEMI and NSTEMI-ACS patients. The percentage of patients without ACS varied across the different types of recommendations (e.g., 14% of patients recruited in the control arm of RCTs cited in class I recommendations had no ACS) (**Figure 3, panels E-F**).

Eligibility criteria and baseline characteristics

There were 23.2% RCTs which excluded patients based on an upper limit for age. Among the 407 RCTs, 55 (13.5%) restricted the inclusion of patients to those younger than 80 years of age, and 11 (2.7%) restricted the inclusion to those older than 70. Patients with chronic kidney disease, on hemodialysis or on anticoagulation were broadly excluded (**Table 1** lists the main exclusion criteria).

Baseline characteristics were analysed for the control arm of each RCT. **Table 2** summarises these baseline characteristics and their availability across the whole set of 407

RCTs. The mean age of the enrolled patients was 62.1±6.3 years. There was a total of 208,564 women recruited between all control groups, representing 29.9% of the control population. Enrolled patients were predominantly white (80.1%), though this data was only available in 26.1% of the RCTs.

Invasive approach and reperfusion management

Overall, 184,815 patients underwent percutaneous coronary intervention (PCI) in the control arms of the RCTs (42.7%). This information was only available in 65.8% of RCTs (aligned with the number of RCTs not including ACS patients). These data did not vary substantially by type of recommendation in both STEMI and NSTEMI-ACS guidelines (**Figure 4 A-B**). There were major differences in the numbers and types of reperfusion therapies in RCTs included in the STEMI (ACC/AHA and ESC) guidelines. The majority of patients with STEMI in the control groups of these RCTs were treated with fibrinolysis (113,552 patients), followed by a primary PCI (34,645 patients). Hence, the number of patients who underwent fibrinolysis was 3.3-fold higher than those who underwent primary PCI. Differences in reperfusion therapy by recommendation type are shown in **Figure 4 C-D**.

Observed endpoints

All-cause mortality and major nonfatal cardiovascular events in the control group were collected and classified into 4 categories according to the follow-up period of each RCT: (a) up to 72h after randomisation, (b) between 72h and 1 month, (c) between 1 month and 1 year, and (d) >1 year. All-cause mortality percentages were 4.7%, 6.6%, 11.9%, and 8.3%, respectively. Non-fatal myocardial infarction percentages were 3.4%, 3.9%, 4.8%, and 5.0%, respectively. Non-fatal stroke percentages were 0.5%, 0.8%, 1.0%, and 2.8%, respectively. Information on these endpoints in the control groups was available in 333 (82.0%) RCTs for all-cause mortality, 291 (72.9%) RCTs for non-fatal MI, and 195 (48%) RCTs for non-fatal stroke.

Sensitivity analyses

Further evaluations were made to compare representativeness between RCTs published before and after year 2000 (Supplementary material online, Table S1), as well as between randomized studies supporting ESC and ACC/AHA CPGs (Supplementary material online, Table S2), and between RCTs supporting STEMI and NSTEMI-ACS CPGs (Supplementary material online, Table S3).

DISCUSSION

The main findings of this analysis can be summarized as follows: (1) less than 20% of all references in ACS guidelines were primary reports of RCTs; (2) the majority of referenced RCTs recruited patients in North-America and Europe, with other regions largely underrepresented; (3) only 68.6% of referenced RCTs enrolled patients with ACS, with the remaining RCTs enrolling patients with other conditions and 19.6% of referenced RCTs actively excluding patients with ACS; (4) there was underrepresentation of some important groups of patients, including elderly, female and non-white patients; (5) the incidence and type of reperfusion used in the control groups of the referenced RCTs was not representative of current clinical practice; and (6) all-cause mortality in the referenced RCTs was largely higher than current standards.

CPGs are grounded on objective, high-quality evidence, and influence the care provided to millions of people worldwide. Cardiologists report CPGs to be their main resource for clinical decision-making.¹⁷ The main findings of this study do not aim to challenge this evidence-based paradigm. Rather, they emphasise the need to evaluate RCTs supporting CPGs in the light of their limitations. Due to the accrual of evidence over time, there is an unavoidable gap between the broad scope of guidelines recommendations and the narrow representativeness provided by the RCTs which support them.

RCTs, especially large cardiovascular outcome trials, and meta-analyses combining their findings, represent the pinnacle of evidence-based medicine.¹⁹ RCTs have greatly contributed to improvements in cardiovascular health on a global scale, and have been pivotal in shaping the evidence-based cardiovascular policies that are employed by decision-makers. Across a number of cardiovascular subfields, adherence to guideline recommendations translates the treatment benefits demonstrated in high quality RCTs to improved patient outcomes in clinical practice.^{20–23}

Cardiovascular outcome trials have become increasingly globalized in recent decades.⁵ The inclusion of participants from many different regions of the world ensures timely recruitment and improves the generalizability of results beyond Western Europe and Northern America. In our study, most RCTs supporting CPGs recruited patients in North America and Europe (52.6% and 73.2% respectively), whereas other regions were largely underrepresented (25.3% in Asia, 20.4% in Latin-America, 19.9% in Australia, and 12.8% in Africa). These figures raise issues about whether the impact of some interventions might vary across regions (wide geographical differences has been described at patient-level in terms of genetic background, concomitant comorbidities and medications, but also at health care system-level in terms of ischemic time delays, and the prevalence and/or type of reperfusion therapy).^{24,25} Event rates have also been described to vary across regions, which might have implications when interpreting any potential heterogeneity in treatment effect.²⁶ One concerning point of the geographic-based findings in this analysis is that they may lead to questioning regarding the applicability of the trial results to all regions of the world. However, it should be acknowledged that this situation is now changing with the contemporary implementation of global RCTs.^{27–30}

Only 68.6% of referenced RCTs enrolled patients with ACS, with the remaining 31.4% RCTs enrolling patients with other conditions. Of note, 19.6% of referenced RCTs actively excluded patients with ACS. Although this number of RCTs not recruiting patients with ACS

might seem alarmingly high, this deviation can be easily explained in many occasions. For example, the majority of RCTs supporting the use of beta-blocker treatment on patients with ACS and heart failure and/or left ventricle dysfunction excluded an ACS population, but chronic coronary syndrome or patients after 1-3 months of an ACS could be included.³¹⁻³⁴ CPGs included this evidence in the secondary prevention section, extrapolating this evidence to post-ACS patients. Some evidence primarily obtained for patients with heart failure with reduced ejection fraction was also used in CPGs for those post-ACS patients with systolic dysfunction (e.g., mineralocorticoid receptor antagonists trials like RALES and EMPHASIS-HF).³⁵⁻³⁷ In other occasions, RCTs without ACS patients were cited to contextualise, but the subsequent addition of other RCTs including ACS patients was then used to specifically address the management in ACS population. This might be the case for the recommendation table dealing with antithrombotic therapy in patients with ACS and atrial fibrillation, which included RCTs recruiting patients only with atrial fibrillation (e.g., ARISTOTLE)³⁸ and RCTs with patients with both atrial fibrillation and ACS (e.g., AUGUSTUS).²⁷

Although age, sex, and race/ethnicity are important factors when generalizing the findings of RCTs to routine practice, the representation of these groups in the evidence supporting contemporary CPGs for ACS had not been previously defined. In line with previous reports, some relevant groups were underrepresented. In some cases, the eligibility criteria specifically excluded some subgroups (23.2% had restrictive entry criteria for older people, resulting in a mean age of 62.1 years for RCTs participants). In other cases, underrepresentation could be identified by evaluating either percentages (women represented less than 30% of the patient recruitment) or the availability of the data (racial/ethnic data was only available in 26.1% of RCTs, and when available there was an overwhelming percentage of white people enrolled in RCTs). Our data confirm previous reports showing that some subgroups have been historically underrepresented and sometimes undertreated.^{6,39,40} A previous systematic review supports these findings, concluding that older

patients, women and non-white patients are still underrepresented in contemporary ACS trials compared with epidemiologic studies with real-world patients.⁴¹

The incidence and type of reperfusion reported in our set of RCTs were both far below modern clinical practice. Contemporary ACS registries have reported that between 70-80% of patients are treated invasively with PCI, but only 42.7% of patients in the RCTs evaluated in our analysis underwent PCI. In modern clinical practice, fibrinolysis is the treatment in ~ 0.3-6% of STEMI patients,^{21,23,42} whereas the number of those who underwent fibrinolysis was 3.3-fold higher than those who underwent primary PCI in our set of RCTs. The registry-based findings are in accordance with current STEMI guideline (both ESC and ACC/AHA) recommendations in which primary PCI strategy is recommended over fibrinolysis in the majority of clinical scenarios.^{10,12} However, we cannot ignore the fact that many of the referenced RCTs were conducted before primary PCI was the standard of care. This information should be taken into account when considering the limitations of some CPG recommendations, and in order to tailor clinical decision-making in some scenarios not well represented by CPGs. This concept is applicable to many other arenas. With the exception of the COMMIT trial,⁴³ all RCTs testing the benefits of beta-blocker treatment within the first 24h after ACS were performed in the pre-PCI era. This does not mean that these recommendations on β -blocker use are not evidence-based – it means that the therapies received by the patients recruited in RCTs supporting those recommendations does not match the current standard of care, and therefore we cannot be 100% certain about what would be the impact on clinical outcome of using beta-blockers in the current context.⁸

In our analysis, the overall all-cause mortality was 11.9% for those studies with a reported follow-up between 1 month and 1 year. In contrast, registries recruiting real-world patients over the last ten years have shown that with a follow-up between 6 month and 1 year, all-cause mortality was about 3-6%.^{21,44,45} Since advances in the management of patients with ACS likely explains this significant improvement in prognosis⁴⁶, the question that

immediately arises is whether the treatment effects would be the same in patient less prone to die. With such a drop in all-cause mortality, the number needed to treat [NTT] for some old therapies would be higher now than at the time when the RCTs were conducted, and therefore perhaps less relevant in the context of current background therapies. Nevertheless, a scenario where each intervention is re-tested under the standard of care is unfeasible and therefore CPGs report on the best evidence currently available.⁴⁶

It is expected for next CPGs to better reflect the full spectrum of patient representativeness, since more recent international RCTs are replacing old studies with less heterogenous populations. Although this change mostly relies on the type of evidence that is generated nowadays, scientific societies also play a pivotal role by making this need more evident in their CPGs (e.g., stressing differences between men and women, or including special population sections might stimulate trialists to be more inclusive in their studies). As suggested by the ESC CPG for STEMI,¹² there is a need for pragmatic real-life clinical trials to avoid selective RCTs precluding universal implementation. The popularisation of pragmatic clinical trials including, registry-based RCTs, is also expected to improve representativeness in CPGs.

Limitations

Our study should be considered within the context of its limitations. First, we focused only on ESC and ACC/AHA CPGs for ACS because we felt many countries adopted their recommendations, but we left aside other CPGs with might yield different findings. This might be relevant for those scientific societies with a different approach in developing their CPGs (e.g, Canadian Cardiovascular Society). Second, some RCTs might have been counted ≥ 2 times in comparisons between recommendations (e.g., one RCT might be part of a recommendation with a LOE A, and in a separate recommendation of LOE B). Therefore, some of the most relevant RCTs might be overrepresented in our aggregated patient-level analyses. Finally, we only evaluated primary publications of RCTs, and did not appraise observational data. It must be acknowledged that it is an impossible task to conduct RCTs addressing all the complex

clinical scenarios that confront physicians. Despite the imperfections of registry data, registries have the potential to provide a different type of evidence as well as to confirm the applicability and generalisability of some findings yielded by RCTs.⁴⁷ Of note, registry-based RCTs were considered RCTs in our assessment (e.g., TASTE trial).

CONCLUSIONS

The main findings of our assessment of the evidence yielded by RCTs cited in ACS guidelines focuses on representativeness, and can be summarized as follows: (1) RCTs represented less than a fifth of all references in ACS guidelines; (2) most RCTs recruited patients in North-America and Europe, whereas other regions were largely underrepresented; (3) about one third of RCTs did not enrol patients with ACS; (4) some important groups of patients were underrepresented (mainly older patients, women and non-white patients); (5) the incidence and type of reperfusion reported in these RCTs was far below current clinical practice; and (6) all-cause mortality was largely higher than current standards. Our conclusions do not aim to challenge the current evidence-based paradigm, but rather emphasise the need to critically appraised the representativeness of RCTs supporting CPGs. CPGs influence the care provided to millions of people worldwide, and it should be understood that guidelines are not rules for, but rather guides to, high quality, evidence-based care.

ACKNOWLEDGMENTS

None.

FUNDING

This project has received funding to cover the electronic case report form from the Balearic Society of Cardiology (Sociedad Balear Cardiología) through the “Bernat Nadal Ginard” grant.

CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

ORIGINAL UNEDITED MANUSCRIPT

REFERENCES

1. Bonow RO, Braunwald E. The Evidence Supporting Cardiovascular Guidelines: Is There Evidence of Progress in the Last Decade? *JAMA* 2019; 321: 1053–1054.
2. Sheridan DJ, Julian DG. Achievements and Limitations of Evidence-Based Medicine. *J Am Coll Cardiol* 2016; 68: 204–213.
3. Solomon SD, Pfeffer MA. The Future of Clinical Trials in Cardiovascular Medicine. *Circulation* 2016; 133: 2662–2670.
4. Pocock SJ, Gersh BJ. Do current clinical trials meet society's needs?: a critical review of recent evidence. *J Am Coll Cardiol* 2014; 64: 1615–1628.
5. Vaduganathan M, Samman Tahhan A, Greene SJ, et al. Globalization of heart failure clinical trials: a systematic review of 305 trials conducted over 16 years. *Eur J Heart Fail* 2018; 20: 1068–1071.
6. Rossello X, Ferreira JP, Caimari F, et al. Influence of sex, age and race on coronary and heart failure events in patients with diabetes and post-acute coronary syndrome. *Clin Res Cardiol* 2021; 110: 1612–1624.
7. Szummer K, Wallentin L, Lindhagen L, et al. Relations between implementation of new treatments and improved outcomes in patients with non-ST-elevation myocardial infarction during the last 20 years: experiences from SWEDEHEART registry 1995 to 2014. *Eur Heart J* 2018; 39: 3766–3776.
8. Rossello X, Raposeiras-Roubin S, Latini R, et al. Rationale and design of the pragmatic clinical trial tREatment with Beta-blockers after myOcardial infarction withOut reduced ejection fracTion (REBOOT). *Eur Heart J Cardiovasc Pharmacother* 2022; 8: 291–301.

9. Rossello X, Pocock SJ, Julian DG. Long-Term Use of Cardiovascular Drugs: Challenges for Research and for Patient Care. *J Am Coll Cardiol* 2015; 66: 1273–1285.
10. O’Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of st-elevation myocardial infarction: A report of the American college of cardiology foundation/american heart association task force on practice guidelines. *J Am Coll Cardiol*; 61. Epub ahead of print 29 January 2013. DOI: 10.1016/j.jacc.2012.11.019.
11. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; 64: e139–e228.
12. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018; 39: 119–177.
13. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021; 42: 1289–1367.
14. Tricoci P, Allen JM, Kramer JM, et al. Scientific evidence underlying the ACC/AHA clinical practice guidelines. *JAMA* 2009; 301: 831–841.
15. Fanaroff AC, Califf RM, Windecker S, et al. Levels of Evidence Supporting American College of Cardiology/American Heart Association and European Society of Cardiology Guidelines, 2008-2018. *JAMA* 2019; 321: 1069–1080.

16. Gaudino M, Hameed I, Rahouma M, et al. Characteristics of Contemporary Randomized Clinical Trials and Their Association With the Trial Funding Source in Invasive Cardiovascular Interventions. *JAMA Intern Med* 2020; 180: 993–1001.
17. van Dijk WB, Grobbee DE, de Vries MC, et al. A systematic breakdown of the levels of evidence supporting the European Society of Cardiology guidelines. *Eur J Prev Cardiol* 2019; 26: 1944–1952.
18. Fanaroff AC, Fudim M, Califf RM, et al. Levels of evidence supporting drug, device, and other recommendations in the American Heart Association/American College of Cardiology guidelines. *Am Heart J* 2020; 226: 4–12.
19. Pocock SJ, Clayton TC, Stone GW. Design of Major Randomized Trials: Part 3 of a 4-Part Series on Statistics for Clinical Trials. *J Am Coll Cardiol* 2015; 66: 2757–2766.
20. Mercado-Lubo R, Yarzebski J, Lessard D, et al. Changing Trends in the Landscape of Patients Hospitalized With Acute Myocardial Infarction (2001 to 2011) (from the Worcester Heart Attack Study). *Am J Cardiol* 2020; 125: 673–677.
21. Puymirat E, Simon T, Cayla G, et al. Acute Myocardial Infarction: Changes in Patient Characteristics, Management, and 6-Month Outcomes Over a Period of 20 Years in the FAST-MI Program (French Registry of Acute ST-Elevation or Non-ST-Elevation Myocardial Infarction) 1995 to 2015. *Circulation* 2017; 136: 1908–1919.
22. Krämer C, Meisinger C, Kirchberger I, et al. Epidemiological trends in mortality, event rates and case fatality of acute myocardial infarction from 2004 to 2015: results from the KORA MI registry. *Ann Med* 2021; 53: 2142–2152.
23. Simonsson M, LarsWallentin L, Alfredsson J, et al. Temporal trends in bleeding events in acute myocardial infarction: insights from the SWEDHEART registry. *Eur Heart J* 2020; 41: 833–843.

24. Rosselló X, Huo Y, Pocock S, et al. Global geographical variations in ST-segment elevation myocardial infarction management and post-discharge mortality. *Int J Cardiol* 2017; 245: 27–34.
25. Bueno H, Rossello X, Pocock S, et al. Regional variations in hospital management and post-discharge mortality in patients with non-ST-segment elevation acute coronary syndrome. *Clinical Research in Cardiology* 2018; 107: 836–844.
26. Pfeffer MA, Claggett B, Assmann SF, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. *Circulation* 2015; 131: 34–42.
27. Lopes RD, Heizer G, Aronson R, et al. Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation. *N Engl J Med* 2019; 380: 1509–1524.
28. Davies JE, Sen S, Dehbi H-M, et al. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. *N Engl J Med* 2017; 376: 1824–1834.
29. Steg PG, Bhatt DL, Simon T, et al. Ticagrelor in Patients with Stable Coronary Disease and Diabetes. *N Engl J Med* 2019; 381: 1309–1320.
30. Mehta SR, Wood DA, Storey RF, et al. Complete Revascularization with Multivessel PCI for Myocardial Infarction. *N Engl J Med* 2019; 381: 1411–1421.
31. Hjalmarson Å, Goldstein S, Fagerberg B, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. *JAMA* 2000; 283: 1295–1302.
32. Packer M, Coats AJS, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001; 344: 1651–1658.

33. Dargie HJ, Lechat P. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999; 353: 9–13.
34. Flather MD, Shibata MC, Coats AJS, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005; 26: 215–225.
35. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999; 341: 709–717.
36. Zannad F, McMurray JJV, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011; 364: 11–21.
37. Rossello X, Ferreira JP, Pocock SJ, et al. Sex differences in mineralocorticoid receptor antagonist trials: a pooled analysis of three large clinical trials. *Eur J Heart Fail* 2020; 22: 834–844.
38. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; 365: 981–992.
39. Rossello X, Ferreira JP, Pocock SJ, et al. Sex differences in mineralocorticoid receptor antagonist trials: a pooled analysis of three large clinical trials. *Eur J Heart Fail* 2020; 22: 834–844.
40. Rossello X, Mas-Lladó C, Pocock S, et al. Sex differences in mortality after an acute coronary syndrome increase with lower country wealth and higher income inequality. *Rev Esp Cardiol (Engl Ed)* 2022; 75: 392–400.
41. Tahhan AS, Vaduganathan M, Greene SJ, et al. Enrollment of Older Patients, Women, and Racial/Ethnic Minority Groups in Contemporary Acute Coronary Syndrome Clinical Trials: A Systematic Review. *JAMA Cardiol* 2020; 5: 714–722.

42. Stähli BE, Roffi M, Eberli FR, et al. Temporal trends in in-hospital complications of acute coronary syndromes: Insights from the nationwide AMIS Plus registry. *Int J Cardiol* 2020; 313: 16–24.
43. Chen Z, Pan H, Chen Y, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005; 366: 1622–1632.
44. Aliprandi-Costa B, Morgan L, Snell LC, et al. ST-Elevation Acute Myocardial Infarction in Australia-Temporal Trends in Patient Management and Outcomes 1999-2016. *Heart Lung Circ* 2019; 28: 1000–1008.
45. Rossello X, Bueno H, Pocock SJ, et al. Predictors of all-cause mortality and ischemic events within and beyond 1 year after an acute coronary syndrome: Results from the EPICOR registry. *Clin Cardiol* 2019; 42: 111–119.
46. Rossello X, Pocock SJ, Julian DG. Long-Term Use of Cardiovascular Drugs: Challenges for Research and for Patient Care. *J Am Coll Cardiol* 2015; 66: 1273–1285.
47. Rossello X, Massó-van Roessel A, Chioncel O, et al. EURObservational Research Programme: a bibliometric assessment of its scientific output. *Eur Heart J Qual Care Clin Outcomes* 2022;8(8):804-811.

ORIGINAL UNEDITED MANUSCRIPT

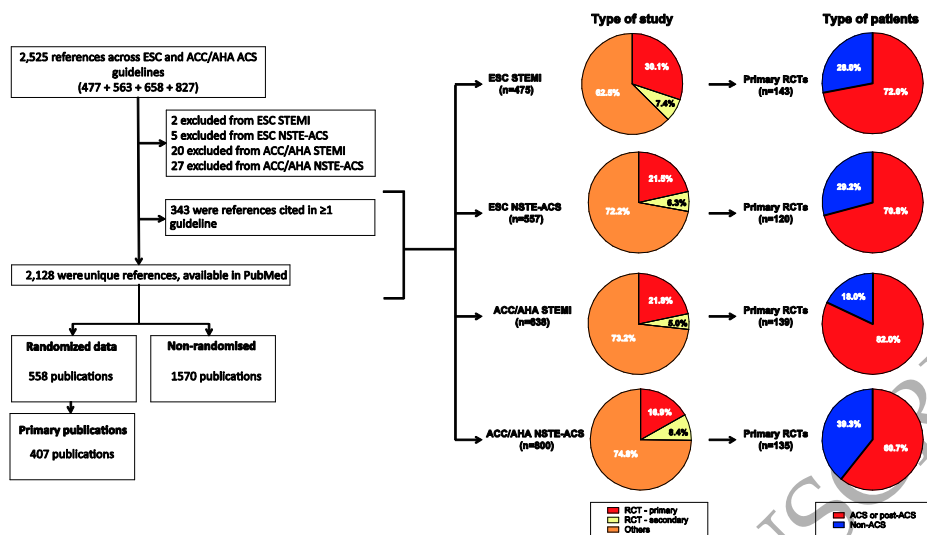


Figure 1. Flow chart, type of studies and type of patients by guideline

The left side of the figure displays the flow chart describing the screening, and selection process of references and RCTs across guidelines. In the middle, there are four pie charts displaying the type of studies by guidelines. In the right side, there are four pie charts showing the type of patients included in RCTs of each guideline.

ACC/AHA: American College of Cardiology/American Heart Association; ACS: acute coronary syndrome; ESC: European Society of Cardiology; NSTEMI-ACS: non-ST-elevation acute coronary syndrome; RCT: randomised clinical trial; STEMI: ST-elevation myocardial infarction.

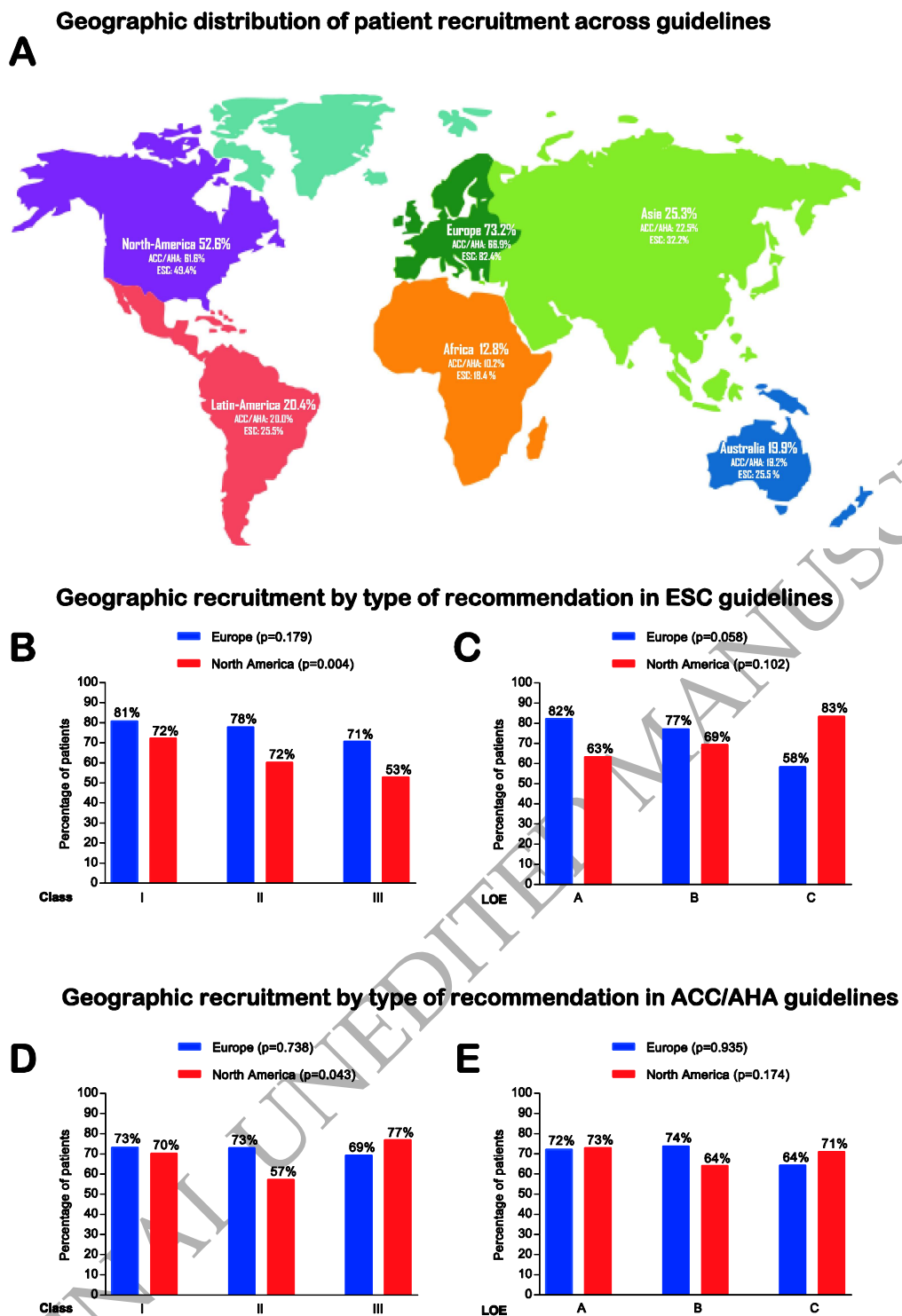


Figure 2. Geographic representativeness across RCTs cited in CPGs

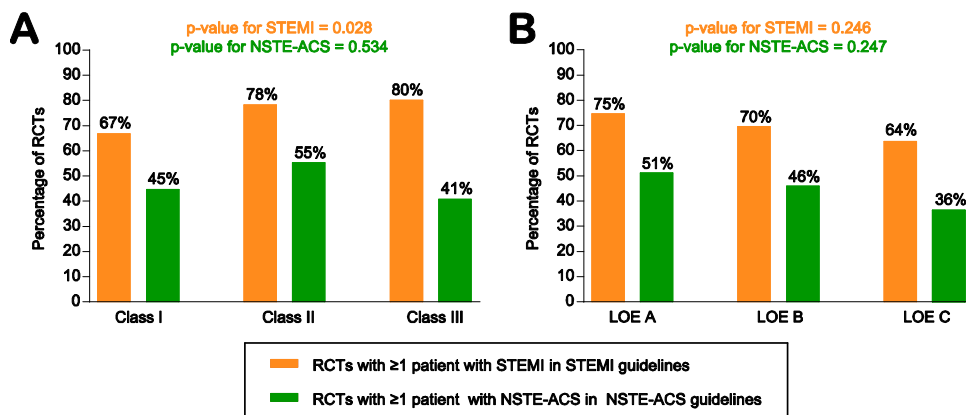
ORIGINAL MANUSCRIPT

Panel A shows the percentage of RCTs recruiting participants from each continent, globally and by type of guidelines (ACC/AHA vs. ESC). Geographic recruitment by recommendation (class and LOE) for ESC guidelines is shown in panels B and C, whereas for ACC/AHA guidelines are shown in panels D and E. P-values are yielded by statistical tests comparing percentages of RCTs recruiting participants from a given region across either class of recommendations or LOEs (e.g., in the ESC guidelines, the percentage of RCTs recruiting patients in North-America was higher for class I than for class II or III recommendations, with a p-value of 0.004).

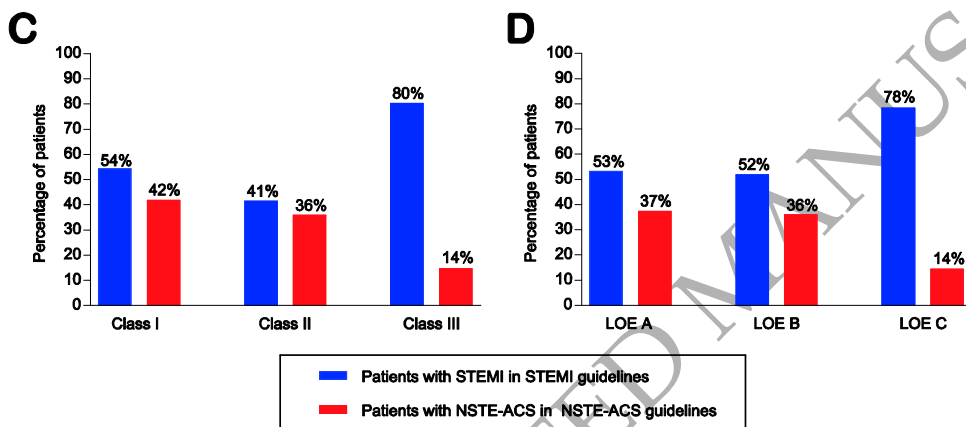
ACC/AHA: American College of Cardiology/American Heart Association; CPGs: clinical practice guidelines; ESC: European Society of Cardiology; LOE: level of evidence; RCT: randomised clinical trial.

ORIGINAL UNEDITED MANUSCRIPT

Percentage of RCTs with STEMI and NSTEMI-ACS patients by guideline



Percentage and type of ACS patients by recommendation and guideline



Percentage of patients without ACS by type of recommendation

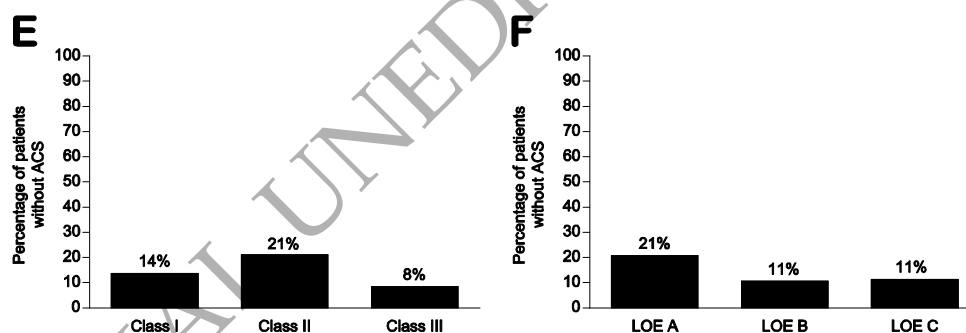
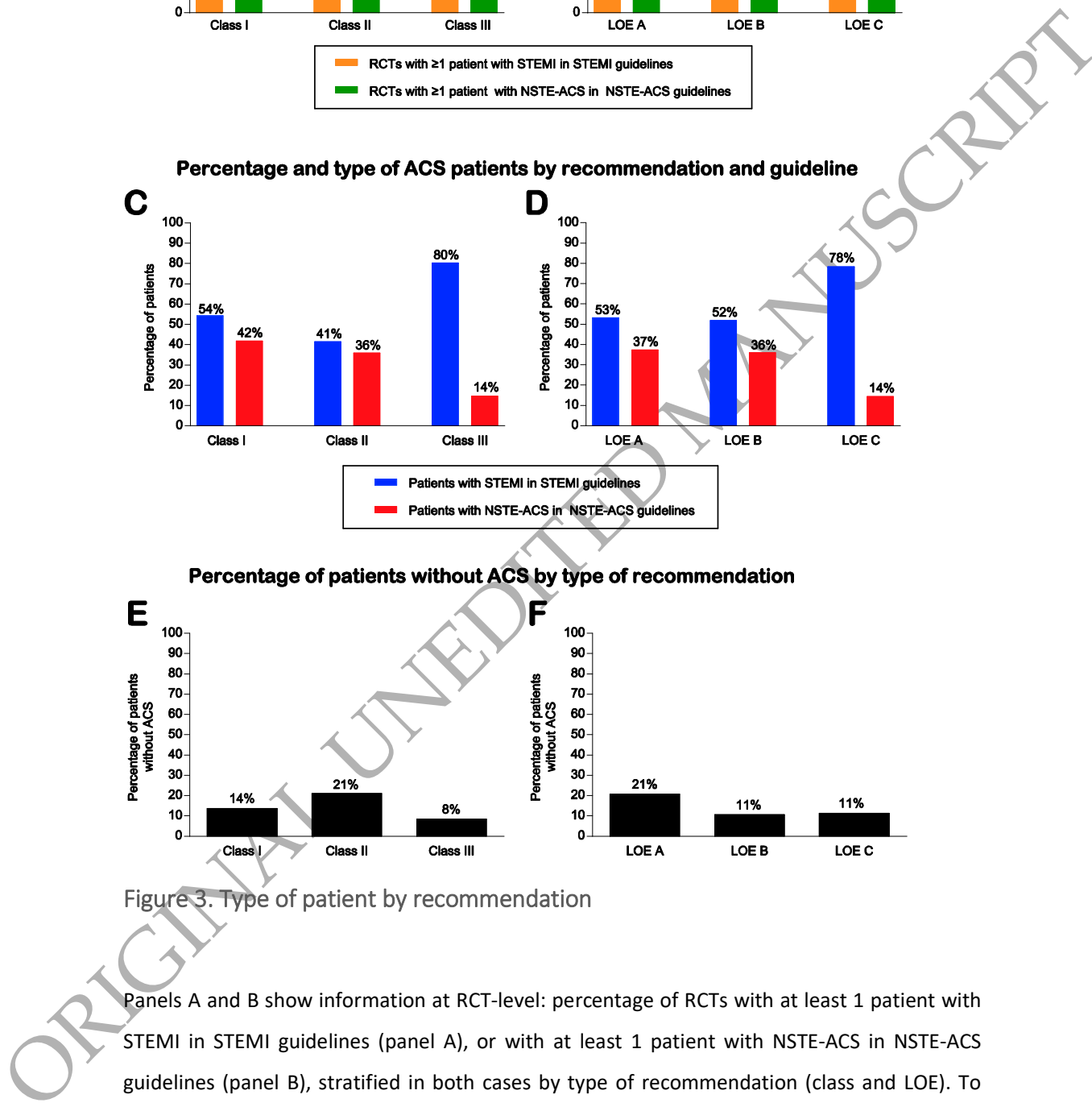


Figure 3. Type of patient by recommendation

Panels A and B show information at RCT-level: percentage of RCTs with at least 1 patient with STEMI in STEMI guidelines (panel A), or with at least 1 patient with NSTEMI-ACS in NSTEMI-ACS guidelines (panel B), stratified in both cases by type of recommendation (class and LOE). To

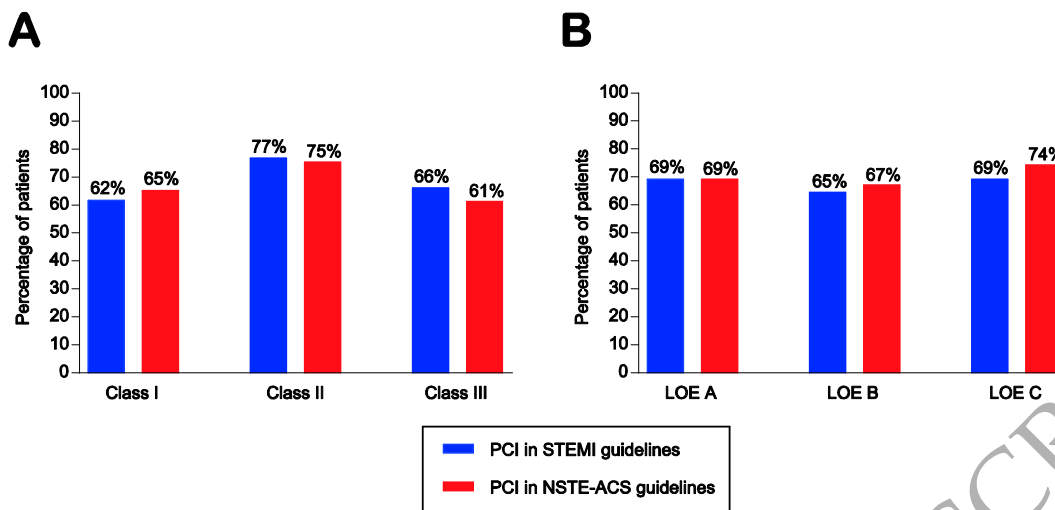


interpret p-values, we can use the information provided in panel A as an example: the percentage of RCTs enrolling patients with STEMI in the STEMI guidelines (both ESC and ACC/AHA) was significantly different by classes of recommendations (I, 67%; II, 78%; III, 80%; $p=0.028$), but not across LOEs (A, 75%; B, 70%, C 64%; $p=0.246$). Panels C to F show information at aggregated patient-level. Panels C and D show the percentage and type of ACS patients stratified by recommendation (i.e., percentage of STEMI patients in recommendations for STEMI patients and percentage of NSTEMI-ACS in recommendations for NSTEMI-ACS patients). Panels E and F show the percentage of patients without ACS stratified by recommendation (class and LOE).

ACC/AHA: American College of Cardiology/American Heart Association; ACS: acute coronary syndrome; ESC: European Society of Cardiology; LOE: level of evidence; NSTEMI-ACS: non-ST-elevation acute coronary syndrome; RCT: randomised clinical trial; STEMI: ST-elevation myocardial infarction.

ORIGINAL UNEDITED MANUSCRIPT

Percentage of patients who underwent PCI by guideline type



Percentage and type of patients with STEMI who underwent reperfusion

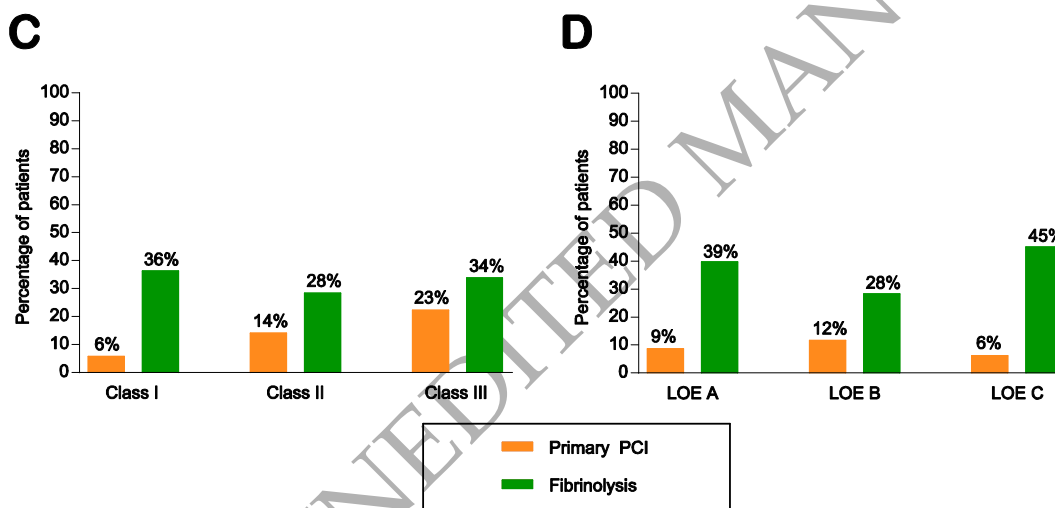


Figure 4. Invasive management in RCTs cited in recommendations

This figure shows information at aggregated patient-level about invasive management in RCTs cited in recommendations. Panels A and B display the percentage of patients who underwent PCI in STEMI and NSTEMI-ACS guidelines stratified by recommendation (class and LOE). Panels C

ORIGINAL UNEDITED MANUSCRIPT

and D shows the percentage of patients with STEMI who underwent reperfusion with primary PCI or with fibrinolysis, by recommendation (class and LOE).

LOE: level of evidence; NSTEMI-ACS: non-ST-elevation acute coronary syndrome; PCI: percutaneous coronary intervention; RCTs: randomised clinical trials; STEMI: ST-elevation myocardial infarction.

ORIGINAL UNEDITED MANUSCRIPT

Table 1. Exclusion criteria in RCTs

Exclusion criteria	Percentage of RCTs using the exclusion criterion (n=407)
Age (upper limit)	23.2%
Upper limit of 70 years old	2.7%
Upper limit of 80 years old	13.5%
Haemodialysis, %	33.5%
Chronic kidney disease, %	32.0%
On anticoagulation excluded, %	26.5%
Liver disease, %	18.9%
Cerebrovascular disease, %	16.7%
Severe valve heart disease, %	13.0%
Prior CAD, %	8.4%
Anaemia, %	8.1%
Respiratory disease, %	5.9%

Categorical variables are expressed as percentages.

CAD: coronary artery disease; RCT: randomised clinical trial

Table 2. Baseline characteristics of the control groups

Variable	All RCTs (n= 407)	Availability of the data among RCTs (%)
Age (years), mean \pm SD	62.1 \pm 6.3	96.1
Female sex, %	29.9	97.5
White race, %	80.7	26.1
Current smoker status, %	31.0	67.0
Hypertension, %	58.9	80.1
Diabetes, %	28.6	84.7
Dyslipidaemia, %	48.8	48.5
Previous CHD, %	32.9	81.8
Prior revascularization, %	27.7	56.9
Previous history of HF, %	16.5	30.5
Cerebrovascular disease, %	9.8	33.5
Peripheral artery disease, %	10.2	22.7
Chronic kidney disease, %	16.3	17.0
Killip I class, %	80.0	21.0

Continuous variables are expressed as mean \pm standard deviation (SD), whereas categorical variables are expressed as percentages.

CHD: coronary heart disease; HF: heart failure; RCT: randomised clinical trial.