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Type of Evidence supporting ACC/AHA and ESC Clinical Practice Guidelines for Acute Coronary Syndrome

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ABSTRACT

Aim:

The aim of clinical practice guidelines for ST elevation myocardial infarction (STEMI) and non-ST elevation acute coronary syndrome (NSTE-ACS) is to assist healthcare professionals in clinical decision-making. We evaluated the type of studies supporting these guidelines and their recommendations.

Methods:

All references and recommendations in the 2013 and 2014 ACC/AHA and 2017 and 2020 (ESC clinical guidelines for STEMI and NSTE-ACS were reviewed. References were classified into meta-analyses, randomised, non-randomised, and other types (e.g., position papers, reviews). Recommendations were classified according to class and their level of evidence (LOE).

Results:

We retrieved 2128 non-duplicated references: 8.4% were meta-analyses, 26.2% randomised studies, 44.7% non-randomised studies, and 20.7% 'other' papers. Meta-analyses were based on randomised data in 78% of cases and used individual-patient data in 20.2%. Compared to non-randomised studies, randomised studies were more frequently multicentre (85.5% *vs.* 65.5%) and international (58.2% *vs.* 28.5%). The type of studies supporting recommendations varied as per the LOE of the recommendation. For LOE-A recommendations, the breakdown of supporting recommendations was: 18.5% meta-analyses, 56.6% randomised studies, 16.6% non-randomised studies and 8.3% 'other' papers; for LOE-B this breakdown was 9%, 39.8%, 38.2%, and 12.9%; and for LOE-C; 4.6%, 19.3%, 30.3%, and 45.9%.

Conclusions:

The references supporting the ACC/AHA and ESC guidelines on STEMI and NSTE-ACS consisted of non-randomised studies in ~45% of cases, with less than a third of the references consisting of meta-analyses and randomised studies. The type of studies supporting guideline recommendations varied widely by the LOE of the recommendation.

Keywords: Evidence-based medicine; Clinical Practice Guidelines, Acute coronary syndrome, Recommendations.

INTRODUCTION

Acute coronary syndromes (ACS), consisting of both ST-segment elevation myocardial infarction (STEMI), and non-ST-segment elevation acute coronary syndrome (NSTE-ACS), represent a significant cause of morbidity and mortality worldwide [1, 2]. Using an evidence-based framework, the American College of Cardiology Foundation/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC) provide clinical practice guidelines (CPGs) to guide the management of patients with STEMI and NSTE-ACS [3–6]. CPGs support the clinical decision-making process and influence the care provided to millions of patients across the world [7, 8]. The importance of this influence is demonstrated by the fact that adherence to CPGs recommendations has been shown to translate into better clinical outcomes [9–11].

Although CPGs are based on the best available scientific evidence, less than 15% of recommendations in cardiovascular CPGs are level of evidence (LOE) A (i.e., supported by data derived from multiple randomised clinical trials or meta-analyses of such studies) [12–14]. Both researchers and clinicians could benefit from a better understanding of the type of studies (e.g.., randomized or non-randomized data, metanalyses) supporting the text and recommendations of CPGs. This may be particularly relevant in complex clinical situations that cannot feasibly be addressed in randomised clinical trials (RCTs). Little research has been performed on the critical appraisal of the scientific evidence supporting CPGs. Some of the previously published reports have primarily chosen to focus on tabulating the number of recommendations according to their class and LOE [12, 13], or on evaluating the LOE based on the type of management (e.g., recommendations regarding therapeutic or diagnostic approaches)[14] or the type of funding [15]. Hence, little is known about the type of studies cited in ACC/AHA and ESC CPGs for ACS. This key information may be useful in allowing healthcare professionals to better interpret the evidence underlying CPG recommendations.

RCTs and meta-analyses are central to the paradigm of evidence-based medicine, and key to understanding the recommendations provided by CPGs. However, observational studies have also an important role, particularly in providing evidence for clinical situations that cannot be randomised[16]. Observational data is also often far more readily available than randomised data, with medical journals publishing many more observational studies than RCTs. In this context, this current analysis aims to determine: (1) the type of evidence supporting ACC/AHA and ESC CPGs for ACS, as well as their basic

study design characteristics; (2) the type of recommendations and their underlying class and LOE, and (3) the link between the types of recommendation and their supporting evidence (e.g., type of studies cited).

METHODS

Selection of guidelines

We obtained the latest versions of CPGs for ACS as of January 1, 2022 from the ACC and ESC websites. The following ACC/AHA and ESC CPGs for ACS were reviewed: the 2013 ACC/AHA Guideline for the management of STEMI [6] and the 2014 ACC/AHA guideline for the management of patients NSTE-ACS [3], the 2017 ESC guideline for the management of STEMI[4] and the 2020 ESC guideline for the management NSTE-ACS[5]. Focused updates were not included in this analysis because their supporting references were not covering the full spectrum of the disease, and these were therefore not considered representative of the evidence for either STEMI or NSTE-ACS.

Data Extraction

Data collection and analysis was performed according to the PRISMA guidelines[17]. From each CPG document, two reviewers (J.S. and L.B.) independently screened and extracted all non-duplicated references using a predesigned electronic form. To identify duplicates, we used the PubMed Identifier (PMID). References were classified by another reviewer (X.R.) into four types of studies: (1) meta-analyses; (2) randomised studies (primary publications of RCTs, or secondary publications of RCTs preserving randomisation)[18]; (3) non-randomised studies (either observational or RCTs not using randomised data); and (4) other papers (consensus papers, other CPGs, reviews). This classification procedure was verified by a second reviewer (either J.S. or L.B.). Any disagreements over the classification of a paper were resolved by consensus after discussion between the three authors (J.S., L.B., and X.R.).

Data extraction for each reference consisted of at least the year of publication, and the medical journal. Then, different information was collected based on the type of study. For meta-analyses, we evaluated their type of data (at individual-patient level *vs.* pooled data *vs.* network), the type of included studies (randomised, observational, or both), and their sample size. For primary and secondary publications of RCTs, as well as for observational studies, we extracted information about whether the study was performed at international- or national-level, whether it was multi-centre or single-centre, and

whether the data were collected prospectively or retrospectively. For both primary publications of RCTs and observational studies, data on the study sample size was collected. For primary publications of RCTs testing for superiority, the p-value was also retrieved. For secondary publications of RCTs, regardless of whether they were using randomised data or not, sample size or p-values were not retrieved in order to avoid overrepresenting studies with multiple secondary publications.

The recommendations provided by each guideline was extracted by two independent reviewers. Each recommendation was presented in the document with a statement (recommendation text), and an associated class and LOE [3–6]. Briefly, Class I recommendations are given for interventions that should be performed, class II are given for reasonable interventions, whereas class III recommendations represent interventions with no benefit or harm. Regarding LOE, type A identifies data derived from ≥2 RCTs, or meta-analyses, LOE B indicates recommendations from a single RCT, or large non-randomised studies, whereas LOE C is based on consensus opinion of experts, or small observational studies. Further details about definitions of class of recommendation and LOE are shown in **Supplementary Table 1.**

In addition to evaluating all references cited in the four documents, we also identified the set of references supporting the recommendations, and linked the information obtained at study-level with the information obtained at recommendation-level. This system allowed us to broadly evaluate the type of studies supporting each class of recommendation, and whether each LOE was adequately supported by relevant references (e.g., for LOE A, ≥2 RCTs, or meta-analyses).

Statistical Analysis

Basic descriptive data was presented for each type of study cited in the four CPGs. Continuous variables are presented as medians with associated interquartile ranges (IQR), whereas categorical variables are presented using frequencies and percentages. A visual inspection of continuous data revealed a non-normal distribution of most continuous variables, and therefore we used nonparametric methods to make comparisons between groups. The Mann-Whitney U test was used for comparisons between 2 groups, whereas the Kruskal-Wallis test was used for comparisons between ≥3 groups. Categorical variables were compared using either the χ^2 or the Fisher exact test as appropriate. Histograms were used to plot and summarise some key continuous data, such as sample size. The characteristics of the type of studies are described as per their classes of recommendations and LOEs.

Two-sided significance testing was used and a p-value <0.05 was considered significant. All analyses were performed using Stata version 16.1 (Stata Corp, College Station, Texas, USA).

RESULTS

Study Characteristics of the references cited in the CPGs

There were a total of 2525 references among the four CPGs. Of these, 54 were excluded from the analysis (primarily due to a lack of PMID), and 343 were duplicated references (**Figure 1**). After exclusion of these, 2128 references were included in the analysis. Some references were cited in more than one CPG: 1011 (47.5%) references were cited in the CPGs for STEMI management (either ESC, ACC/AHA, or both) and 1292 (60.7%) were cited in CPGs for NSTE-ACS management (either ESC, ACC/AHA, or both). The number of references which were cited in all four CPGs was 178 (13.4%).

The breakdown of the identified references as per study type was as follows: 178 (8.4%) were meta-analyses, 407 (19.1%) were primary publications of RCTs, 151 (7.1%) were secondary publications of RCTs (preserving randomised groups in their analyses), 133 (6.3%) were secondary publications of RCTs not using randomised data (i.e., observational-like data), 819 (38.5%) were observational studies, 100 (4.7%) were consensus or position papers, and 340 (16.0%) were other type of papers (CPGs, reviews, research letters, study designs of RCTs, case reports, etc.).

Meta-analyses

Among the 178 meta-analyses identified in the CPGs, 36 (20.2%) used individual patient-data, 133 (74.7%) used summary data, and 9 (5.1%) were network meta-analyses (**Figure 2**). Most meta-analyses were based on randomised data (78% used only data from RCTs). Around 25% of the identified meta-analyses did not contain a single study recruiting more than 1000 patients. There were no differences in the meta-analyses sample size between the three types of meta-analyses (p=0.244). The distribution of the sample sizes of the identified meta-analyses is shown in **Figure 2, panel D.**

A summary of the characteristics of the meta-analyses according to the class of recommendation and LOE is presented in **Table 1**. The type of data analysed was not significantly different across the class and LOE categories (p=0.205 and p=0.186, respectively). No differences were found in the same regard for the type of studies included. However, the median sample size was significantly higher for LOE C, compared to LOE A and LOE B (p=0.014), but not different as per the different classes of recommendations (p=0.377) (**Table 1**).

Randomised data

There were 558 randomised studies identified in the CPGs (**Figure 3**), of which 151 (27.1%) were secondary publications of RCTs, such as subgroup analyses, secondary endpoints, or post-hoc analyses. For primary publications of RCTs (n=407), the median sample size was 1010 patients (IQR: 270-3682). In comparison to observational data, randomised studies were more frequently international (58.2% *vs.* 28.5%, p<0.001), and multicentre (85.5% *vs.* 65.6%, p<0.001).

At the recommendation-level, the characteristics of the primary publications of RCTs according to class of recommendations and LOE were significantly different, as those published after the year 2000 were more frequently cited for class II and class III recommendations, than for class I (p<0.001) (**Table 2)**. There was a significantly higher number of primary publications of RCTs with a p-value <0.05 among class of recommendation I (75.6%), compared to class II (65.5%) and class III (40.5%). In addition, randomised studies supporting LOE A recommendations tended to have a larger sample size and were more frequently multicentre and international than LOE B and C recommendations.

Non-randomised studies

Of the 952 studies using non-randomised data, 649 (68.2%) had prospectively collected the data, and were mostly multicentre (n=623, 65.6%), and confined to national cohorts (n=679, 71.6%) (**Figure 4**). Overall, the median sample size was 1950 patients (IQR: 372-12097).

The characteristics of the identified non-randomised studies according to class of recommendations and LOE are summarized in **Table 3.** There were no significant differences across classes of recommendations and LOEs with regard to the prospective data collection, international location, and number of centres. However, there were differences in the sample size by type of recommendation, with a larger sample size for LOE A recommendations compared with LOE B (p=0.038), and for class II recommendations in comparison to class I or class III recommendations (p=0.004) (**Table 3**).

Recommendations by class and level of evidence

There were 600 recommendations across the four CPGs addressing STEMI and NSTE-ACS management **(Figure 5, panel A)**: 359 (58.2%) class I, 200 (33.3%) class II and 51 (8.5%) class III. As per LOE, 19%, 44.7%, and 36.3% were A, B, and C, respectively. The distribution of LOE also varied significantly by class of recommendation (p<0.001) (**Figure 5, panel A**). The classes of recommendation and LOEs are summarized for each CPGs in **Figure 5** (**panels B and C**).

Type of studies in the recommendation tables

We further analysed the number and distribution of type of studies as per the classes of recommendation and LOEs. There were some recommendations without references which could not be included in this analysis. This included 92 class I (26.4%), 65 class II (32.5%) and 6 class III (11.8%) recommendations [1, LOE A (0.9%), 2 LOE B (0.8%) and 160 LOE C (73.4%)].

The study types were similarly distributed across the different classes of recommendations (p=0.328) (**Figure 6, panel A**). By contrast, when comparing study types across the different LOE, there were significant differences (p<0.001) (**Figure 6, panel B**). LOE A recommendations were supported mainly by randomised studies (56.6%), followed by meta-analyses (18.5%), non-randomised studies (16.6%), and other papers (8.3%). For LOE B, the corresponding percentages were 39.8%, 9.0%, 38.2%, and 12.9% for randomised studies, meta-analyses, non-randomised studies, and other papers, respectively. For LOE C, percentages were 19.3% and 4.3% for randomised studies and meta-analyses, respectively (**Figure 6, panel B**).

To further evaluate the underlying evidence behind each class of recommendation, we pooled data from the ACC/AHA and ESC CPGs to evaluate the distribution of the type of studies by class of recommendation in NSTE-ACS (**Figure 6, panel C**) and STEMI documents (**Figure 6, panel D**). There was a significant difference in the distribution of the study types as per class of recommendation for NSTE-ACS CPGs (**Figure 6, panel C**), but not for STEMI CPGs (**Figure 6, panel D**).

To further evaluate the underlying evidence behind each LOE, we pooled all references cited in recommendation tables from both the ACC/AHA and ESC guidelines (**Figure 6, panel E**). For both LOE A and LOE B recommendations, the distribution of study types varied significantly across the classes of recommendations (p=0.011 and p=0.036, respectively), whereas a non-statistical significance was found for LOE C. Among LOE A recommendations, class II recommendations were supported more frequently by randomised data (76.5%), than class I recommendations (52.0%). Among LOE B recommendations, class II and class III recommendations were more frequently supported by meta-analyses than class I recommendations.

All the recommendations with references were revised in the light of the number and type of studies cited in their statements. For LOE A recommendations, 79.2% (n=334) had either cited ≥2 meta-analyses or ≥2 RCTs. For LOE B recommendations, 98.3% (n=825) had cited either consensus expert opinion or retrospective observational studies. Among LOE C recommendations, 87.2% (n=95) complied

with the required evidence of consensus expert opinion or retrospective observational studies, while 12.8% (n=14) were supported by randomised data.

DISCUSSION

Main findings

Our study summarises the type of evidence supporting both the text and the recommendations in the ACC/AHA and ESC CPGs for ACS. Around ~45% of all the references in these texts were non-randomised studies, with only a third of the cited studies being randomised studies or meta-analyses. Non-randomised studies were mostly prospective and national, whereas randomised studies had more commonly a multicentre, international study population enrolment. Over two thirds of meta-analyses were based on RCTs and used aggregated data. Regarding the types of recommendation, 19 % were LOE A, and ~70% were either class I or class III recommendations (i.e., to do or to do not). Furthermore, whereas references cited in LOE A recommendations were mostly randomised studies or meta-analyses, LOE B recommendations cited a similar proportion of randomised and non-randomised studies, and LOE C recommendations more commonly cited 'other' papers (e.g., consensus papers). When the references from the recommendation tables in both ACC/AHA and ESC guidelines were pooled and stratified by ACS, class III recommendations in the NSTE-ACS CPGs were more frequently supported by randomised studies and meta-analyses, in comparison to class I recommendations. Taken together, this analysis provides a comprehensive overview of the type of evidence that has been used to produce CPGs for ACS management.

Evidence supporting the documents and the recommendations of the four ACS CPGs

Although CPGs are a key paradigm of evidence-based practice in medicine, few studies have thoroughly evaluated their content. In a previous study evaluating multiple CPGs published between 2008 and 2018 from both the ACC/AHA and ESC CPGs, the number of recommendations supported by either randomised data or meta-analyses was limited to less than 9%, whereas up to 42% of recommendations were based on expert opinion and evidence from smaller registries [12, 13]. In our study which restricted its focus to the STEMI and NSTE-ACS CPGs, the percentages of randomised data and meta-analyses among the whole CPG (not only recommendations) were significantly higher (~30%). Similar conflicting observations have been made in other fields: for KDIGO renal CPGs, RCTs and meta-analyses has been reported to be as low as 4% [19], while for Obstetrics and Gynaecology CPGs it has been reported to be

as high as 37% [20]. The main novelty of our study is the deeper evaluation of the underlying evidence supporting CPGs for ACS. We reported that nearly two-thirds of the references in CPGs for ACS are non-randomised studies (44.7%) or other papers (21%). In an ideal world, all care delivered should be supported by evidence from well-conducted RCTs, whenever they can be performed. However, RCTs can also have some limitations to their use: strict eligibility criteria, low external validity (which has an impact on the generalisability of the findings), and short follow-up periods. In this regard, observational studies may also provide some complementary information, such as a longer follow up, which allows for the detection of rarer outcome events, and a higher generalisability, as patients enrolled in observational studies can be more representative of routine clinical practice [21]. Our analysis highlights that CPGs for ACS (and more specifically, their recommendation tables) are supported not only by randomised data, but also by other types of evidence, such as non-randomised studies, which may often be the best available evidence [16]. Although observational studies have a significant and increasing role in research, RCTs are still considered the gold standard in the evaluation of the safety and efficacy of new treatments. The results of the current analysis are not intended to challenge the validity of CPGs, but rather to highlight the type of evidence that is actually available to guide "evidence based" clinical practice (i.e., the term ''evidence based'' does not always indicate that it is based on randomised data, but rather the best available evidence).

Distribution of recommendations by class and level of evidence

In comparison with previous reports [13, 14], there were a lower percentage of class II recommendations (33%), and a higher percentage of class I recommendations (58%) in our study. A decade ago, Tricoci *et al.* reported a high rate of class II recommendations (up to 40%) when assessing 16 ACC/AHA CPGs.[13] After the evaluation of 27 ESC CPGs, Dijk *et al.* reported the majority of recommendations to be class I (48%) and II (45%)[14]. One potential explanation for our findings is that more evidence has been accrued for ACS than for other cardiovascular conditions. Importantly, the distribution of the classes of recommendations (I *vs.* II *vs.* III), did not vary significantly across the four ACS CPGs, which implies that the interpretation of the body of evidence was largely similar amongst the ACC/AHA and ESC task forces, in contrast to other fields [22]. In contrast, LOE distribution was different in the 2017 ESC STEMI Guideline in comparison to the other CPGs. This may be explained by a shift to uncertainty (the reduction in the number of LOE B recommendations is accompanied by an increase in LOE C). The differences between the 2013 and 2017 CPGs for STEMI, may be explained by:

(a) new evidence emerging but not yet validated by RCTs or the contribution of large observational studies; (b) the introduction of new recommendations on physician and network performances, or non-therapeutic recommendations (such as patient's lifestyle choices); and (c) the willingness to leave more room for good clinical judgment. CPGs are intended to be flexible, and the fact that ACC/AHA and ESC CPGs are generally well-matched and aligned is a sign of consistent interpretation of the best available evidence by the expert task forces.

Grading of the quality of evidence supporting the four ACS CPGs and the type of evidence they are supported by

In addition to the differences in the type of studies by class of recommendations, we also demonstrated differences in the type of evidence supporting each LOE. For LOE A recommendations both randomised and non-randomised studies tended to have a larger sample size in comparison to LOE B and LOE C recommendations. Furthermore, we observed a trend towards a higher percentage of RCTs with a statistically significant primary outcome (i.e., p value <0.05) for LOE A recommendations, in comparison to LOE B. In addition, LOE C recommendations were supported by RCTs in nearly 20% of cases (the majority with a p value <0.05), by non-randomised studies in up to 30% of cases and meta-analyses in 5%. Therefore, expert opinion was the driver of supporting evidence in around half of LOE C recommendations. These results are reassuring with respect to the system for grading LOE in ACC/AHA and ESC. Usually, LOE C demonstrates an uncertainty of evidence[23], but clinicians should be aware that LOE C does not equal no data at all, but rather limited data. In the revised methodology of the ACC/AHA guidelines, LOE C has been further ranked into LOE C-limited data and LOE C- Expert opinion[24].

When the references from the recommendation tables were pooled from both ACC/AHA and ESC CPGs for ACS, there were a higher number of randomised studies and meta-analyses supporting LOE A recommendations than LOE B and C. Although the methodology underlying the development of CPGs is simple and transparent, it is unclear whether the type of study can be the only factor determining the LOE (i.e., grading the quality of the evidence might be also useful). For example, some LOE A recommendations might be based on two small, national, RCTs with very stringent entry criteria, whereas some LOE B may be based on large non-randomised studies showing a consistent and plausible treatment effect [25]. In this regard, the Grading and Recommendations Assessment, Development and Evaluation (GRADE) framework is one of the alternatives to grade the quality and reliability of the evidence

underlying CPGs[26], though it also has some limitations. Our study also highlights that further evidence is needed to improve both STEMI and NSTE-ACS management, given that nearly a third of recommendations were classed as LOE C. This represents a huge opportunity for trialists to fill the knowledge gap and further improve the evidence supporting future CPGs, which should lead to improved outcomes for patients with ACS.

Gaps in evidence and room for improvement

Despite the great advances in STEMI and NSTE-ACS management over recent decades, many recommendations are not based on studies that are at the top of the hierarchy of evidence. In our study, RCTs and meta-analyses were 55% of the citations in recommendations, which is in fact a high percentage compared to guidelines addressing other topics (i.e., ACS has received plenty of attention and funding due to its prevalence and impact on prognosis). Current ESC guidelines report a section for gaps in evidence and areas for future research, which is mostly based on areas lacking randomised data. In the 2017 and 2020 ESC guidelines for STEMI and NSTE-ACS, respectively, Task Forces highlighted the need to assess beta blockers in ACS patients without reduced ejection fraction, or the need to elucidate the optimal timing of coronary angiography and revascularisation strategies. Fortunately, these guideline statements have arisen awareness and have resulted in the initiation of some randomised trials aimed to fill these gaps of evidence [27]. Regarding the use of biomarkers and risk scores in NSTE-ACS, new scientific advances have been triggered in form of observational and meta-analytical research [28, 29]. In addition to address these unmet clinical needs, the focus should be put on the methodology [30] and representativeness [31] of the studies used to support guidelines, as well as in the reduction of position and consensus papers cited to support recommendations.

Limitations

Our study has several limitations. First, we included only the ACC/AHA and ESC CPGs for the management of STEMI and NSTE-ACS patients (i.e., 4 CPGs); thus, the results might not apply to either other regions, or other cardiovascular conditions. Second, in the assessment of the types of studies cited by type of recommendation, we did not differentiate between the direction of the treatment effect for RCTs (i.e., whether the treatment was effective for ≥2 RCTs, or they showed discordant results). Third, references may have been counted ≥2 times in comparisons between recommendations (e.g., one RCT might be supporting a recommendation with a LOE A, and a different one with LOE B). Lastly, the content of all the references in the CPGs is a surrogate for the totality of evidence supporting the CPGs,

but may not be wholly representative of the totality of evidence already available in the literature. However, clinical decision-making is based on CPGs, and therefore the results of our analysis were felt to be a useful surrogate for the evidence supporting the current management of patients with ACS in Europe and North America.

CONCLUSIONS

In the ACC/AHA and ESC ACS guidelines, nearly half of the cited references were non-randomised studies, while only a third were reports from randomised studies or meta-analyses. Regarding the types of recommendation, 19 % were LOE A, and ~70% were either class I or class III recommendations (i.e., to do or to not do). References cited in LOE A recommendations were mostly randomised studies or meta-analyses, LOE B recommendations cited a similar proportion of randomised and non-randomised studies, whereas LOE C cited ~46% of other papers (e.g., consensus papers). More research is needed to provide better evidence to support guideline recommendations and to further improve the outcomes of patients with ACS.

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DECLARATIONS

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FIGURE LEGENDS

Figure 1. Flow chart

Primary publications of randomised clinical trials (*RCTs) and secondary publications of RCTs (preserving the randomised groups) were categorised as randomised studies, whereas secondary analysis of RCTs not using randomised data and all type of observational studies were classified as non-randomised studies. "Other papers" involved position papers, expert consensus, clinical practice guidelines, reviews, research letters, study designs of RCTs, and other types of studies*.

Figure 2. Characteristics of meta-analyses

Panel A summarises the type of meta-analyses based on the type data that was used. Panel B shows the type of studies included in the meta-analyses. Panel C displays the number of studies included with >1000 patients. Panel D illustrates the distribution of the sample size of the meta-analyses. Panel E describes differences of meta-analyses according to the type of guidelines (STEMI vs. NSTE-ACS).

Figure 3. Characteristics of randomised studies

Panel A shows whether the studies were international or national; panel B, shows whether they were single- or multicentre; and panel C summarises the type of publication (primary vs. secondary publications). Panel D shows the distribution of the sample size (this data was only collected for primary publications of RCTs). Panel E describes differences in the identified randomised studies according to the type of guideline (STEMI vs NSTE-ACS).

Figure 4. Characteristics of non-randomised studies

Panel A summarises whether the studies were single- or multicentre. Panel B shows whether they were international or national. Panel C illustrates the direction of data collection (retro- vs. prospectively). Panel D shows the distribution of the sample size of non-randomised studies. Panel E describes differences in the identified non- randomised *studies according to the type of guideline (STEMI vs NSTE-ACS).*

Figure 5. Summary of recommendations classes and levels of evidence in the ACC/AHA and ESC guidelines for acute coronary syndrome

Panel A shows the number of recommendations in each guideline, as well as the summary of their class, level of evidence (LOE), and class by LOE. Panel B shows the distribution of the classes of recommendations in each guideline. Panel C describes the distribution of the LOE in each guideline.

Figure 6. Type of study by class of recommendations and level of evidence

For the present analysis, we considered number and type of studies among all references cited in recommendations. Panel A illustrates the study types by classes of recommendation, whereas panel B demonstrates the study types by levels of evidence (LOE). Panels C and D present the differences in percentages of type of studies between the different classes of recommendations, as per the type of ACS guideline (STEMI vs. NSTE-ACS). Panel E shows the number and type of studies among all the references cited in the recommendations, for each class of recommendations, stratified by the LOE.

TABLES

Table 1. Characteristics of meta-analyses according to class of recommendation and level of evidence

	Class of recommendation					Level of evidence			
	I (n=97)	**II (n=44)**	**III (n=14)**	**p-value**		**A (n=78)**	**B (n=75)**	**C (n=5)**	**p-value**
Type of meta-analysis				0.186					0.205
Individual patient data	20 (20.0)	8 (18.2)	0			14 (18.0)	13 (17.3)	1 (20.0)	
Summary data	75 (75.0)	36 (81.8)	14 (100.0)			59 (75.6)	62 (82.7)	4 (80.0)	
Network meta-analysis	5 (5.0)	0	0			5 (6.4)	0	0	
Type of studies included				0.211					0.236
Randomised clinical trials	92 (92.0)	35 (79.6)	12 (85.7)			71 (91.2)	64 (85.3)	4 (80.0)	
Observational studies	2 (2.0)	3 (6.8)	1 (7.1)			2 (2.6)	3 (4.0)	1 (20.0)	
Both	5 (5.0)	6 (13.6)	1 (7.1)			4 (5.2)	8 (10.7)	0	
Sample size	10150 (4433-38153)	7081 (2961-33960)	10150 (6264-145373)	0.377		10234 (4433-33958)	8940 (2962-32350)	145373 (54234-174149)	0.014
No. studies with >1000 patients				0.547					0.147
None	10 (12.2)	8 (19.5)	1 (7.1)			6 (9.4)	13 (19.1)	0	
1-3	29 (35.4)	14 (34.2)	3 (21.4)			25 (39.1)	21 (30.9)	0	
≥4	43 (52.4)	19 (46.3)	10 (71.4)			33 (51.6)	34 (50.0)	5 (100.0)	

Table 2. Characteristics of randomised studies according to class of recommendation and level of evidence

	Class of recommendation					Level of evidence			
	I (n=352)	**II (n=193)**	**III (n=45)**	**p-value**		**A (n=239)**	**B (n=330)**	**C (n=21)**	**p-value**
Year of publication				<0.001					0.079
≤2000	83 (23.6)	18 (9.3)	3 (6.7)			46 (19.3)	51 (15.5)	7 (33.3)	
>2000	269 (76.4)	175 (90.7)	42 (93.3)			193 (80.8)	279 (84.6)	14 (66.7)	
Number of centres				0.178					0.005
Single centre	30 (8.5)	26 (13.5)	5 (11.1)			15 (6.3)	41 (12.4)	5 (23.8)	
Multicentric	322 (91.5)	167 (86.5)	40 (88.9)			224 (93.7)	289 (87.6)	16 (76.2)	
Study cohort				0.012					0.091
National	94 (26.7)	69 (35.8)	20 (44.4)			65 (27.2)	108 (32.7)	10 (47.6)	
International	258 (73.3)	124 (64.3)	25 (55.6)			174 (72.8)	222 (67.3)	11 (52.4)	
Type of publication of randomised data				0.466					0.080
Primary randomised clinical trials	291 (82.7)	156 (80.8)	40 (88.9)			207 (86.6)	262 (79.4)	18 (85.7)	
Secondary randomised clinical trials	61 (17.3)	37 (19.2)	5 (11.1)			32 (13.4)	68 (20.6)	3 (14.3)	
Sample size*	2231 (598 - 1262)	1694 (426-8877)	2958 (600-12092)	0.101		2725 (1004 - 9878)	1810 (365-12092)	1517 (50-3761)	0.002
P value for superiority RCTs *				<0.001					0.063
p-value <0.05	194 (75.6)	93 (65.5)	15 (40.5)			132 (73.7)	155 (64.9)	15 (8.3)	

** p-value for the primary endpoint and sample size were summarised only for primary publications of randomised clinical trials (RCTs).*

Table 3. Characteristics of non-randomised studies according to class of recommendation and level of evidence

	Class of recommendation					Level of evidence			
	I (n=251)	**II (n=144)**	**III (n=25)**	**p-value**		**A (n=70)**	**B (n=317)**	**C (n=33)**	**p-value**
Year of publication				0.013					<0.001
≤2000	39 (15.5)	12 (8.3)	0			0	37 (11.7)	14 (42.4)	
>2000	212 (84.5)	132 (91.7)	25 (100.0)			70 (100.0)	280 (88.3)	19 (57.6)	
Number of centres				0.620					0.195
Single centre	83 (33.1)	44 (30.8)	6 (24.0)			20 (28.6)	98 (31.0)	15 (45.5)	
Multicentre	168 (66.9)	99 (69.2)	19 (76.0)			50 (71.4)	218 (69.0)	18 (54.5)	
Study cohort				0.338					0.073
National	175 (69.7)	90 (62.5)	17 (68.0)			46 (65.7)	208 (65.6)	28 (84.9)	
International	76 (30.3)	54 (37.5)	8 (32.0)			24 (34.3)	109 (34.4)	5 (5.2)	
Data collection									
Prospective	182 (72.5)	105 (72.9)	18 (72.0)	0.983		46 (65.7)	233 (73.5)	26 (78.8)	0.518
Retrospective	66 (26.6)	37 (26.1)	7 (28.0)			21 (31.3)	82 (26.0)	7 (21.2)	
Sample size	1094 (296-7081)	2336 (427-11389)	1967 (743-24112)	0.038		2457 (454-15007)	1345 (352-9461)	200 (89-1572)	<0.001
Large observational studies with >5000 patients	69 (27.8)	49 (34.5)	9 (36.0)	0.322		28 (41.8)	96 (30.5)	3 (9.1)	0.004

ESC and ACC/ACC guidelines for ACS were screened.

2525 refereces were screened.

2128 non-duplicated references were retrieved.

600 recommendations were extracted.

Randomised studies

58.2% were international, and 85.5% multicentre studies.
Most were primary publications of RCTs (72.9%).

Non-randomised studies

28.5% were international, and 65.6% multicentre studies.
Most collected data prospectively (68.5%).

Meta-analyses

20.2% used individual patient data, and 78.0% included only RCTs.
49% included ≥4 studies with >1000 patients.

Other papers

Other guidelines, consensus documents, reviews...

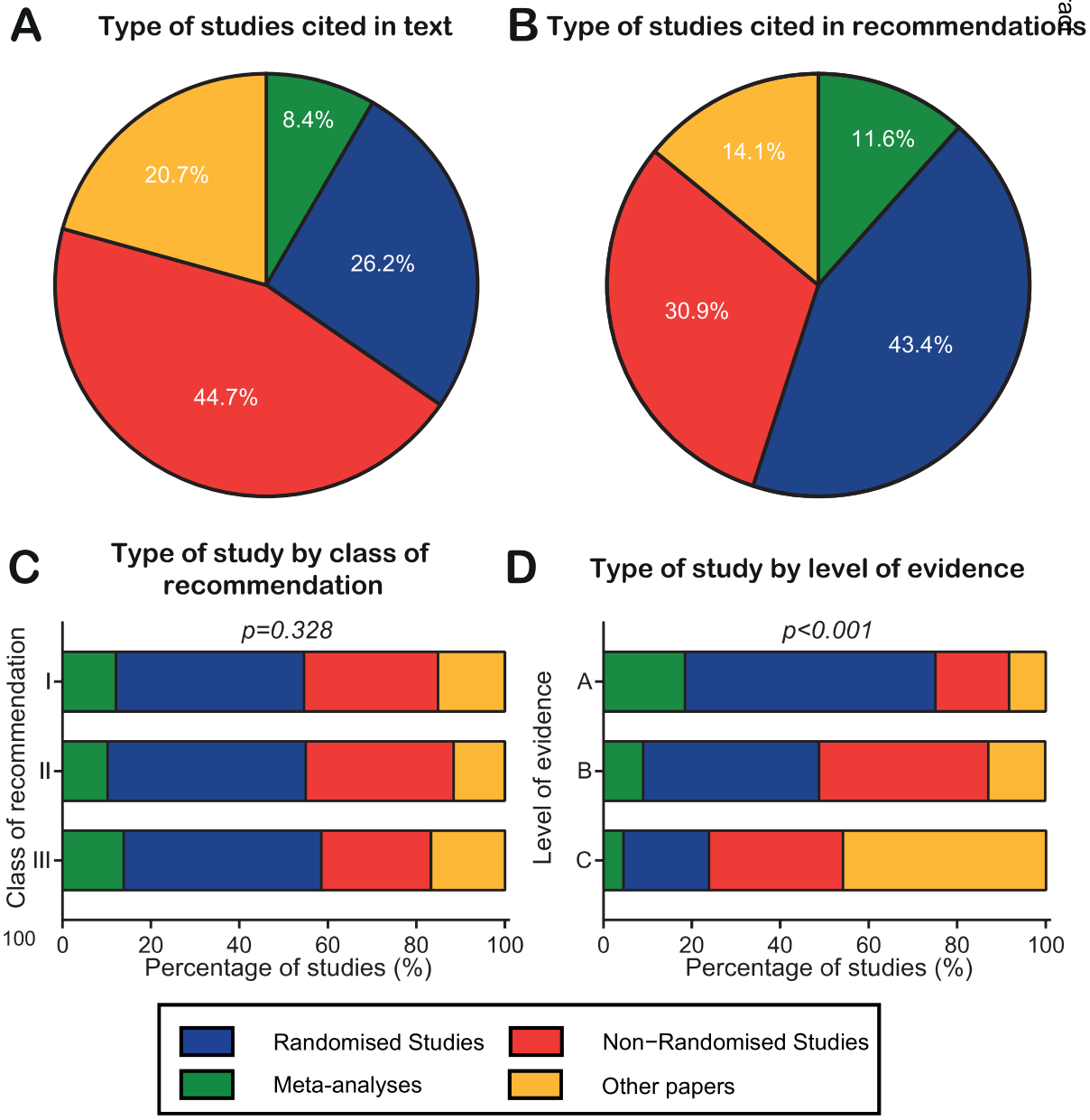


Figure 1

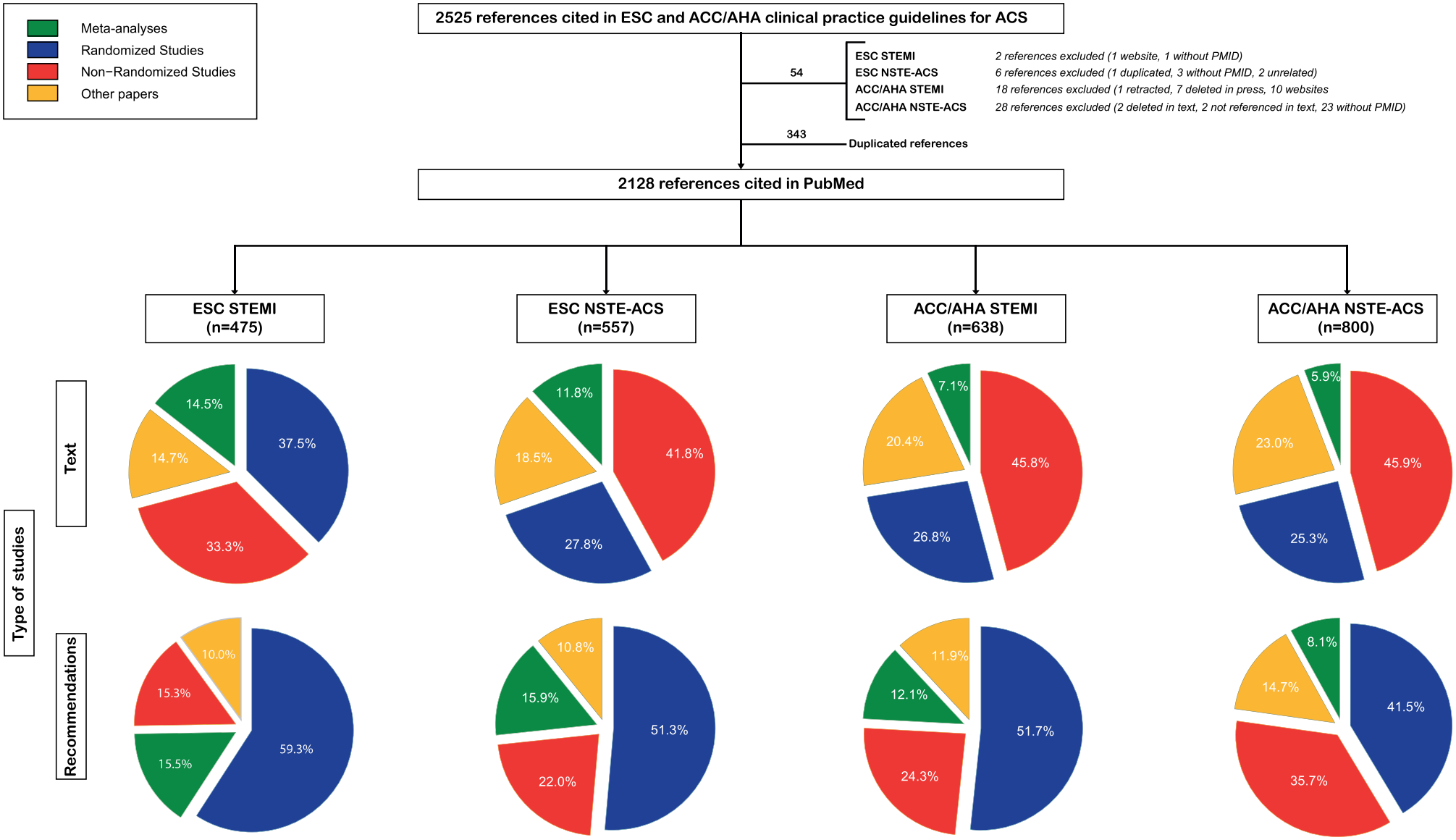
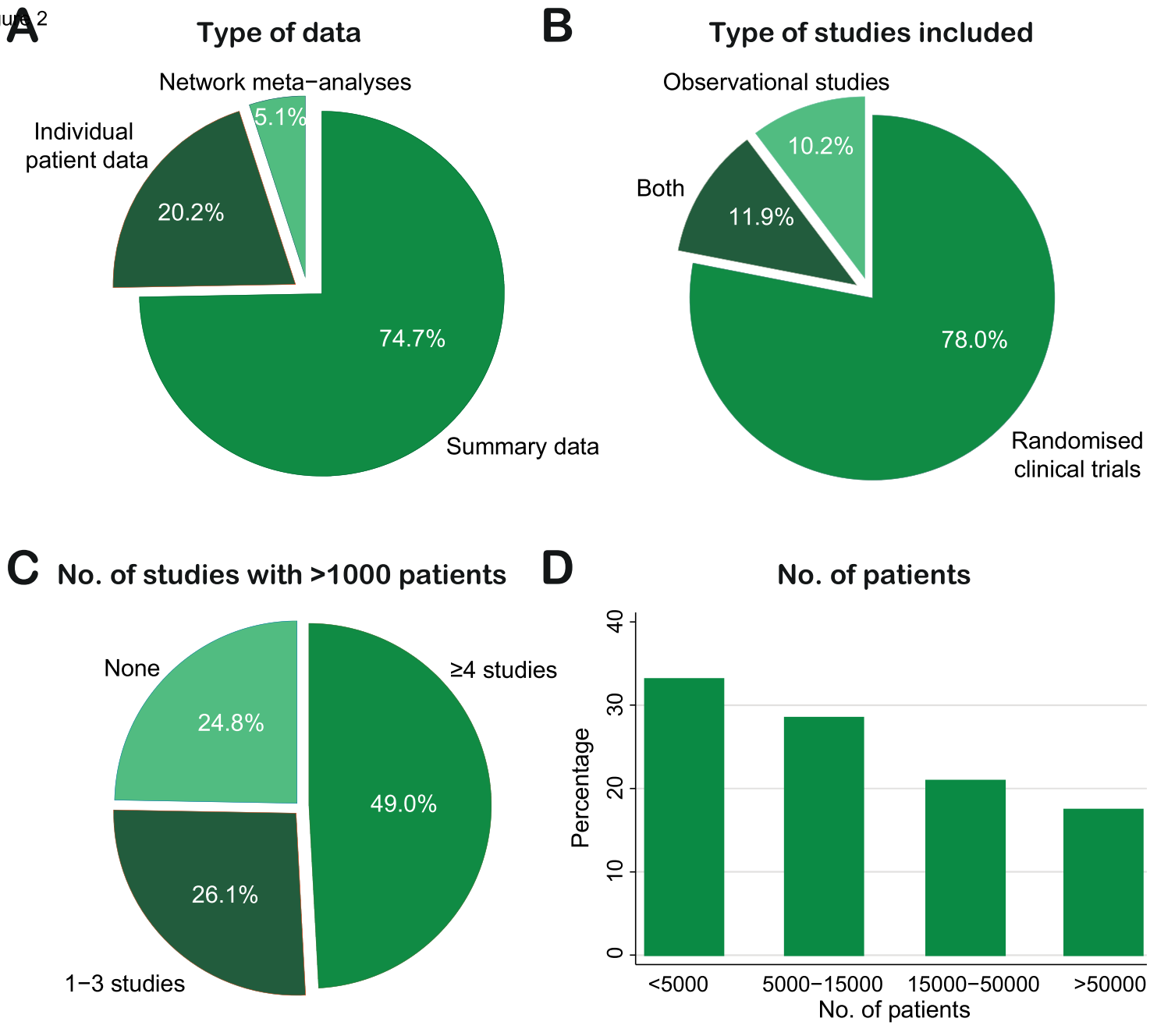

Meta-analyses
Randomized Studies
Non−Randomized Studies
Other papers
2525 references cited in ESC and ACC/AHA clinical practice guidelines for ACS
54
ESC STEMI
ESC NSTE-ACS
ACC/AHA STEMI
ACC/AHA NSTE-ACS
2 references excluded (1 website, 1 without PMID)
6 references excluded (1 duplicated, 3 without PMID, 2 unrelated)
18 references excluded (1 retracted, 7 deleted in press, 10 websites
28 references excluded (2 deleted in text, 2 not referenced in text, 23 without PMID)
343
Duplicated references
2128 references cited in PubMed
ESC STEMI (n=475)
ESC NSTE-ACS (n=557)
ACC/AHA STEMI (n=638)
ACC/AHA NSTE-ACS (n=800)
Type of studies
Text
Recommendations
14.5%
37.5%
14.7%
33.3%
11.8%
41.8%
18.5%
27.8%
7.1%
45.8%
20.4%
26.8%
5.9%
45.9%
23.0%
25.3%
10.0%
59.3%
15.3%
15.5%
10.8%
51.3%
15.9%
22.0%
11.9%
51.7%
12.1%
24.3%
8.1%
41.5%
14.7%
35.7%

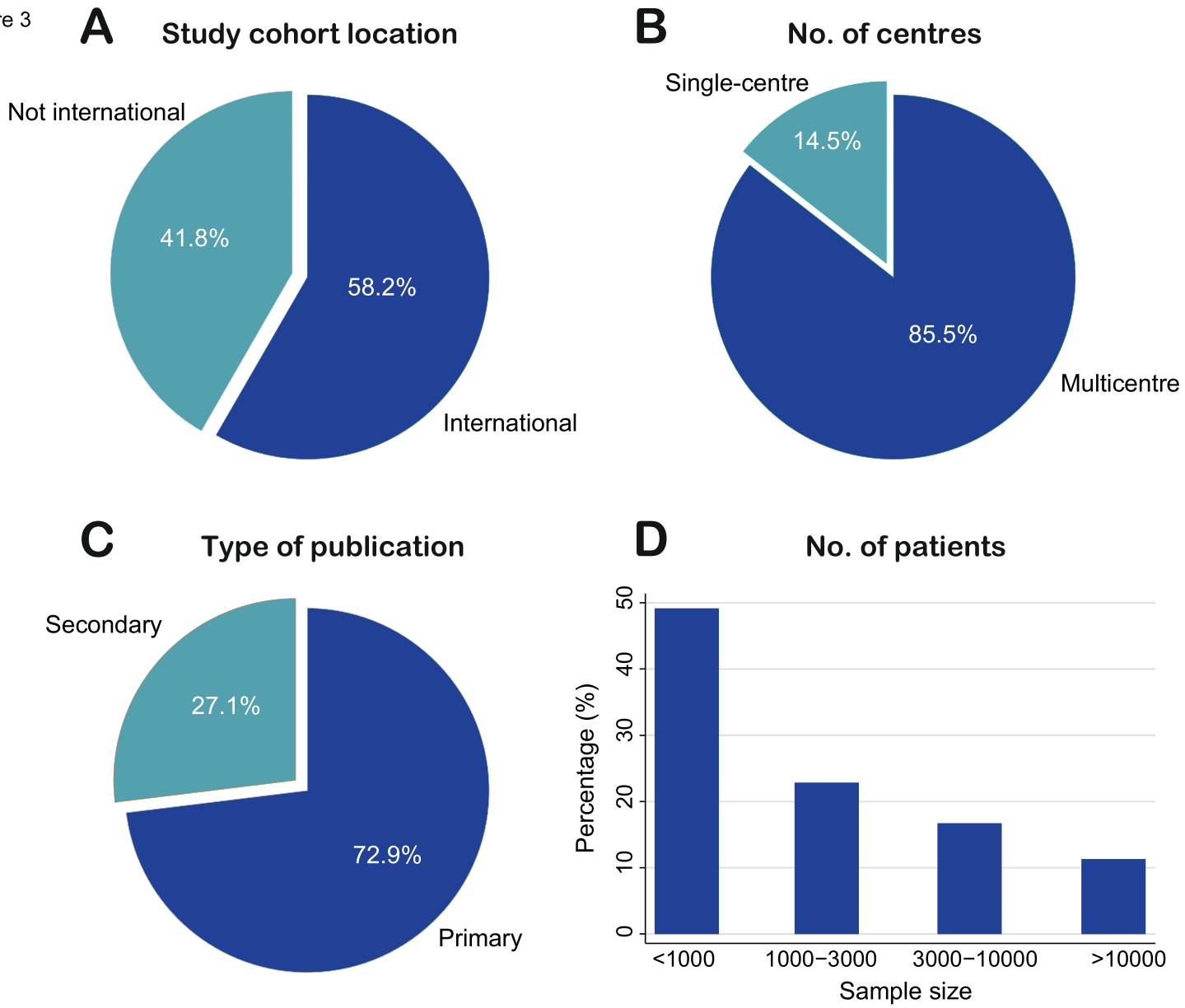
Figure 2



E Summary by type of ACS

	ACC/AHA + ESC guidelines for STEMI (n=97)	ACC/AHA + ESC guidelines for NSTE-ACS (n=102)
Type of data		
Individual patient data	19 (19.6%)	22 (21.6%)
Summary data	74 (76.3%)	74 (72.6%)
Network meta-analyses	4 (4.1%)	6 (5.9%)
Type of studies included		
Randomised clinical trials	79 (81.4%)	77 (76.2%)
Observational studies	8 (8.3%)	12 (11.9%)
Both	10 (10.3%)	12 (11.9%)
Number of studies with >1000 patients		
None	25 (28.7%)	16 (17.8%)
1-3	26 (29.9%)	17 (18.9%)
≥4	36 (41.4%)	57 (63.3%)

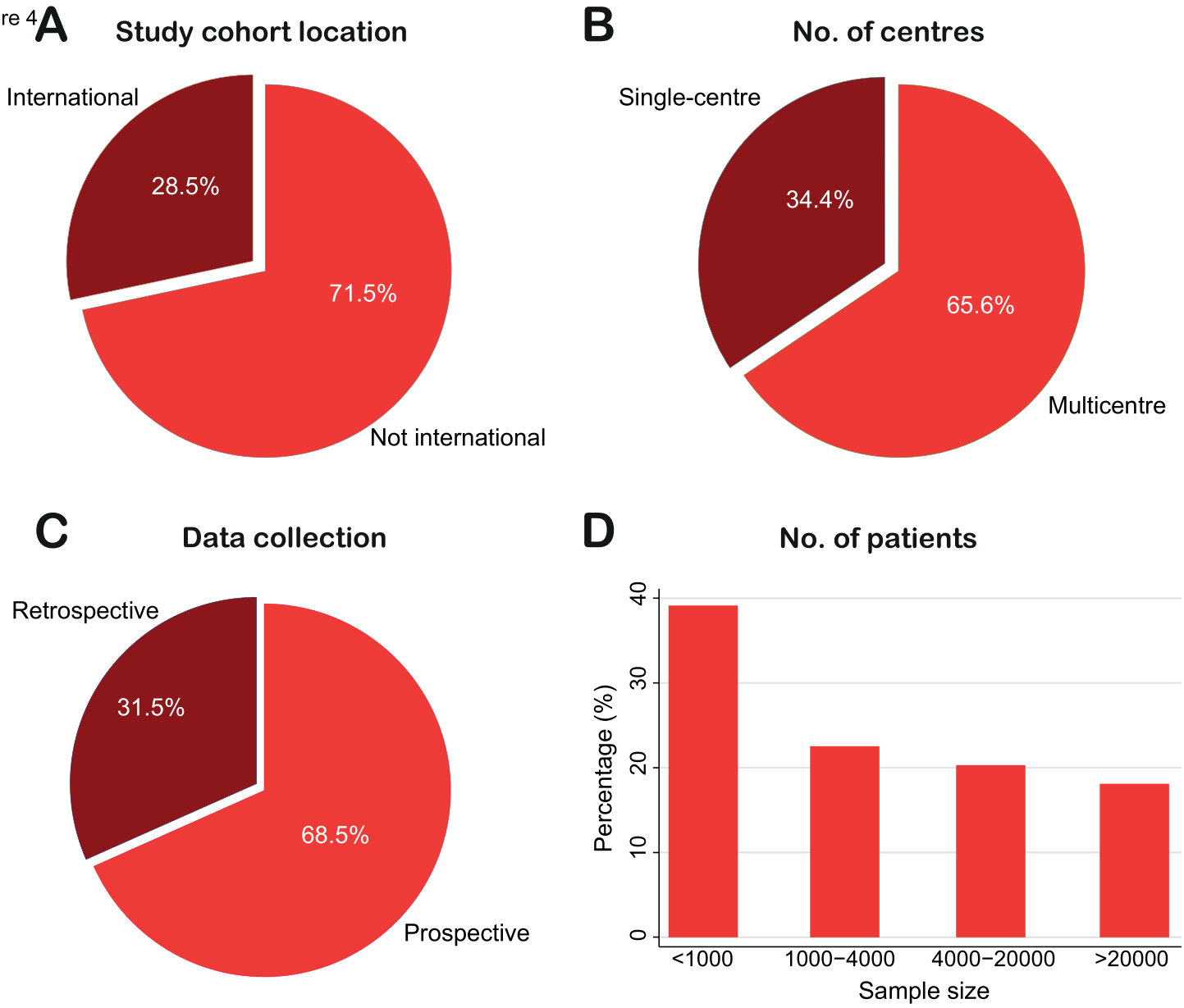
Figure 3



E Summary by type of ACS

	ACC/AHA + ESC guidelines for STEMI (n=292)	ACC/AHA + ESC guidelines for NSTE-ACS (n=327)
Year of publication		
≤2000	65 (22.3%)	62 (19.0%)
>2000	227 (77.7%)	265 (81.0%)
Number of centers		
Single centre	36 (12.3%)	50 (15.3%)
Multicentre	256 (87.7%)	277 (84.7%)
Study cohort		
National	117 (40.1%)	130 (38.8%)
International	175 (59.9%)	197 (60.2%)
Type of publication		
Primary publication	230 (78.8%)	230 (70.3%)
Secondary publication	62 (21.2%)	97 (29.7%)
Sample size		
<500	83 (36.1%)	69 (30.0%)
500-1499	48 (20.9%)	43 (18.7%)
150-2999	32 (13.9%)	42 (18.3%)
3000-7999	29 (12.6%)	34 (14.8%)
≥8000	38 (16.5%)	42 (18.3%)

Figure 4



E Summary by type of ACS

	ACC/AHA + ESC guidelines for STEMI (n=425)	ACC/AHA + ESC guidelines for NSTE-ACS (n=578)
Year of publication		
≤2000	55 (12.9)	63 (10.9)
>2000	371 (87.1)	516 (89.1)
Number of centers		
Single-centre	148 (34.8)	186 (32.2)
Multicentre	277 (65.2)	392 (67.8)
Study cohort		
National	328 (77.2)	387 (67.1)
International	97 (22.8)	190 (32.9)
Data collection		
Prospective	266 (62.7)	419 (72.6)
Retrospective	158 (37.3)	158 (27.4)
Sample size		
<500	142 (33.9)	152 (36.3)
500-2999	112 (26.5)	166 (28.8)
3000-4999	19 (4.5)	42 (7.3)
5000-14999	50 (11.9)	88 (15.3)
≥15000	98 (23.2)	129 (2.4)

Figure 5

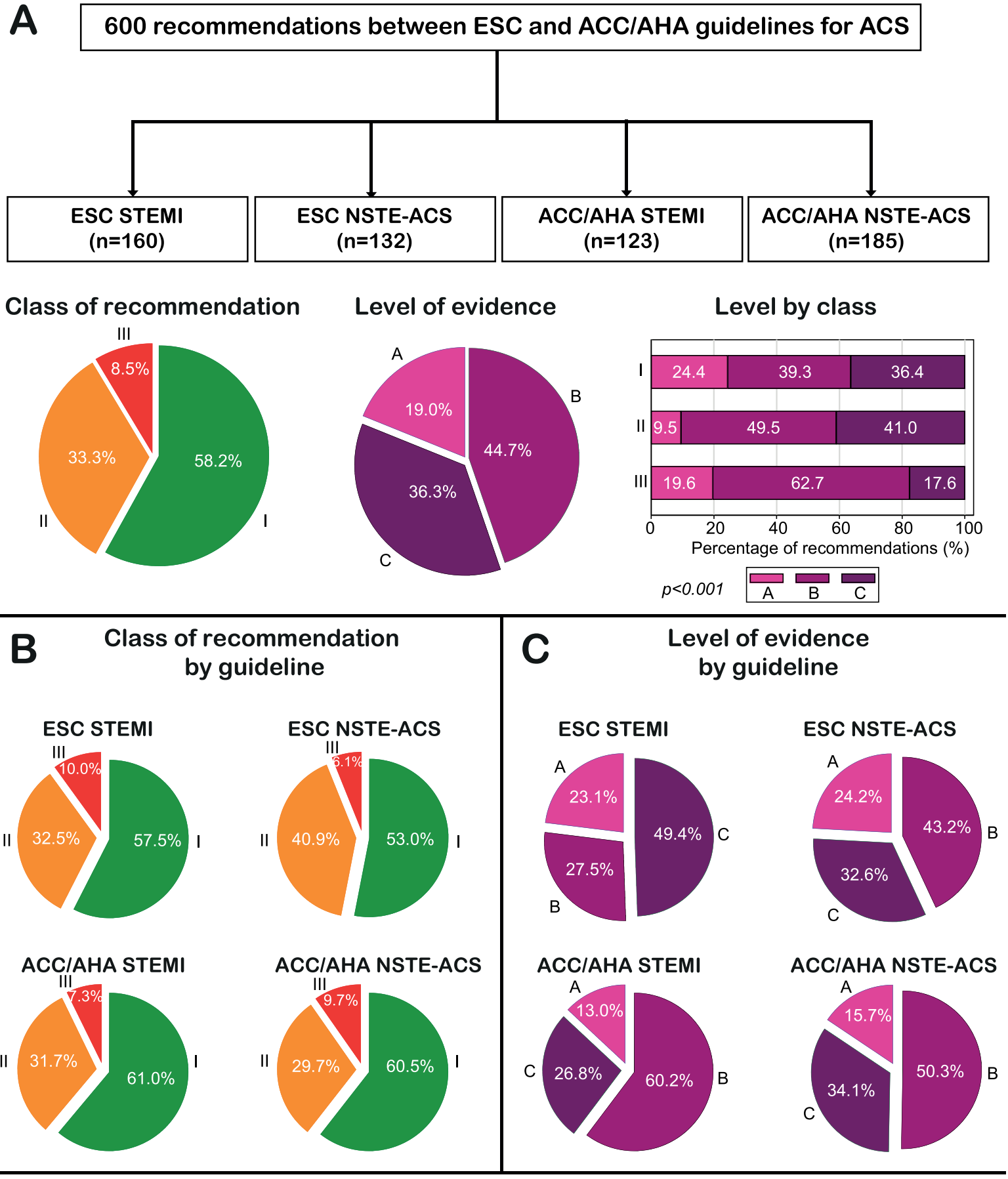
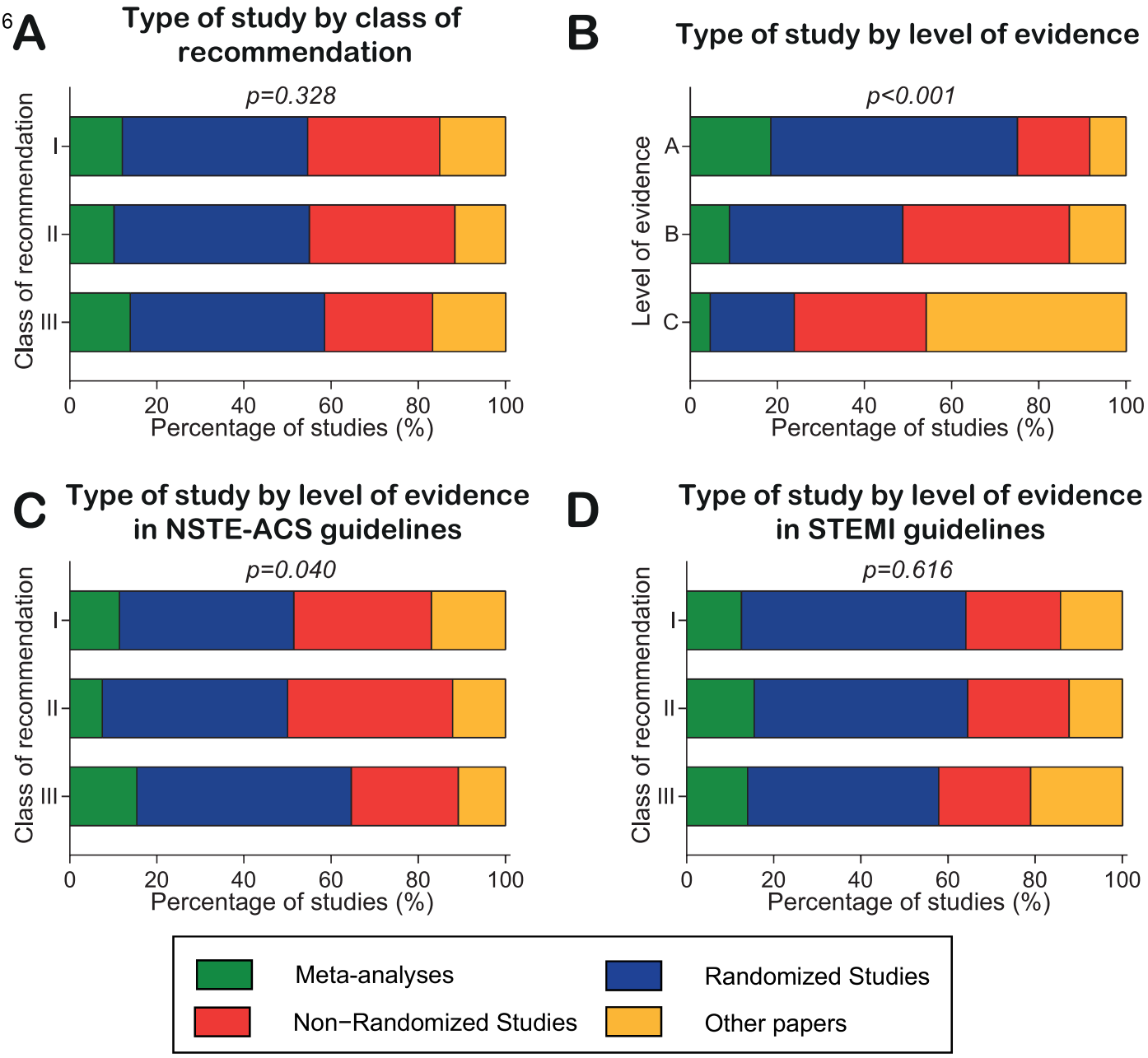

A
600 recommendations between ESC and ACC/AHA guidelines for ACS
ESC STEMI (n=160)
ESC NSTE-ACS (n=132)
ACC/AHA STEMI (n=123)
ACC/AHA NSTE-ACS (n=185)
Class of recommendation
III
8.5%
33.3%
58.2%
II
I
Level of evidence
A
19.0%
B
44.7%
36.3%
C
Level by class
I 24.4 39.3 36.4
II 9.5 49.5 41.0
III 19.6 62.7 17.6
0 20 40 60 80 100
Percentage of recommendations (%)
p<0.001
A B C
B
Class of recommendation by guideline
ESC STEMI
III
10.0%
II
32.5%
57.5%
I
ESC NSTE-ACS
III
6.1%
II
40.9%
53.0%
I
ACC/AHA STEMI
III
7.3%
II
31.7%
61.0%
I
ACC/AHA NSTE-ACS
III
9.7%
II
29.7%
60.5%
I
C
Level of evidence by guideline
ESC STEMI
A
23.1%
49.4%
C
27.5%
B
ESC NSTE-ACS
A
24.2%
43.2%
B
32.6%
C
ACC/AHA STEMI
A
13.0%
C
26.8%
60.2%
B
ACC/AHA NSTE-ACS
A
15.7%
50.3%
B
34.1%
C

Figure 6



E Type of study by class of recommendation and level of evidence

Level of evidence		Class I (n=331)	Class II (n=68)	Class III (n=23)	p-value
A	Randomized Studies	172 (52.0%)	52 (76.5%)	15 (65.2%)	0.011
	Non−Randomized Studies	58 (17.5%)	8 (11.8%)	4 (17.4%)	
	Metaanalyses	69 (20.9%)	7 (10.3%)	2 (8.7%)	
	Other papers	32 (9.7%)	1 (1.5%)	2 (8.7%)	
		(n=428)	(n=326)	(n=75)	
B	Randomized Studies	167 (39.0%)	134 (41.1%)	29 (38.7%)	0.036
	Non−Randomized Studies	169 (39.5%)	127 (39.0%)	21 (28.0%)	
	Metaanalyses	30 (7.0%)	34 (10.4%)	11 (14.7%)	
	Other papers	62 (14.5%)	31 (9.5%)	14 (18.7%)	
		(n=69)	(n=37)	(n=3)	
C	Randomized Studies	13 (18.8%)	7 (18.9%)	1 (33.3%)	0.117
	Non−Randomized Studies	24 (35.8%)	9 (24.3%)	0 (0%)	
	Metaanalyses	1 (1.5%)	3 (8.1%)	1 (33.3%)	
	Other papers	32 (9.7%)	32 (9.7%)	1 (33.3%)	