Coevolutionary analysis of evidence and recommendations in STEMI clinical practice guidelines: A 33-year meta-research study of ACC, AHA, and ESC

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ABSTRACT

Background ST-Segment Elevation Myocardial Infarction (STEMI) is considered the main cause of mortality and morbidity for decades globally. Regularly, cardiology-related medical organizations publish clinical practice guidelines (CPGs) to support healthcare professionals in the diagnosis, management, and prevention of future cardiovascular events. Nevertheless, the level of evidence (LOE) and classification of recommendations (CORs) endorsing STEMI-associated CPGs recommendations have not been systematically appraised.

Purpose This meta-research study evaluated and described the CORs and LOE over time for STEMI guidelines endorsed by the American Heart Association (AHA), American College of Cardiology (ACC), and European Society of Cardiology (ESC), from 1990 to 2023.

Data sources We initially searched on PubMed and AHA/ACC/ESC electronic repositories to obtain STEMI-related CPGs, published from 1990 to 2023, including their immediate predecessors.

Study Selection Guidelines related to acute in-hospital STEMI management were included; recommendations related to unstable angina/Non–STEMI were excluded.

Data Extraction Data management was performed by 2 content experts. Recommendations on pharmacological and nonpharmacological interventions (PI and NPI, respectively) were extracted ipsilaterally, further processed and coded based on thematic analysis fundamentals. Recommendation's recordings associated with each recommendation were maintained as the primary guideline publication without team's specialist judgement. Pharmacological-related recommendations were categorized in accordance with the Anatomical Therapeutic Chemical Classification System by the WHO Collaborating Centre for Drug Statistics Methodology. Changes in the proportion and LOE were evaluated longitudinally, using chi-square test (x^2). Data visualization included heatmaps, linear plots, and Sankey diagrams.

Data Synthesis Twenty-six guidelines (2,139 STEMI-specific recommendations) were evaluated. We observed an overall predominance of recommendations relying on moderate (proportion of 30.1% of LOE-B recommendations) or low (proportion of 28.9% of LOE-C recommendations) quality of evidence over the 33-year span. Only 17.7% of processed recommendations were based on high quality of evidence. Pharmacological interventions were more often LOE-A compared

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with NPI (21.5% vs 13.8%; *P*-value < 0.05). Most abstracted PI related to anticoagulants and dual anti-platelet therapies, while the most frequent category of NPI were related to percutaneous coronary interventions and implantable cardiac devices. Two consecutive guidelines comparison revealed that LOE and COR assigned to corresponding recommendation were minimal.

Limitations Restriction to only AHA/ACC/ESC guidelines and primary focus on acute in-hospital management recommendations.

Conclusions STEMI-related recommendations from foremost cardiology societies worldwide have largely relied on moderate/low-quality evidence, with slight changes over time. Novel ways to generate high quality evidence in a more pragmatic and efficient fashion are warranted.

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Background

Clinical practice guidelines (CPG) are commonly considered as primary sources for obtaining medical knowledge about diagnostic, therapeutic, and prognostic pathways among physicians in a diverse spectrum of medical specialties, particularly in cardiology.[1] In cardiology, 3 nonprofit medical organizations have played a critical role in preparation and dissemination of CPGs.[2,3] During the guideline preparation, consensus-based recommendations receive a classification and level of evidence (class of recommendations [CORs] and level of evidence [LOE], respectively). While the COR categorization system is subcategorized into 5 levels that reflect the balance of benefits and harms for each intervention, the LOE grading scheme reflects the data underlying the referred recommendation. Nowadays, despite crescent adoption of transparent evidence rating systems (including the Grading of Recommendations Assessment, Development and Evaluation [GRADE] approach) in various medical specialties, the main cardiology societies across the globe still remain using a methodology to categorize the evidence based on a 3-leveled classification system (LOE-A, LOE-B, and LOE-C).[4-7] Worldwide, multiple research agendas have assessed cardiovascular guidelines at a macro level to enhance guideline transparency, following primary assessments stressing reliance on low to moderate level of evidence in high-stakes health decisions.[8-12] ST-Elevation Myocardial Infarction (STEMI) requires singular assessment to improve the generation of applicable recommendations, primarily focused on temporal disaggregation of available data substantiating acute in-hospital STEMI recommendations across the full spectrum of therapeutic modalities. Previous umbrella appraisal of recommendations did not allow researchers to differentially evaluate the temporal evolution of multiple health interventions, particularly pharmacological versus nonpharmacological interventions. The evaluation of the evolution of CORs and LOEs, specifically in discerning in-hospital drug- and nondrug-based recommendations for (STEMI) is essential for guideline development refinement, improvement of routine clinical practice, and ultimately enhancing patient-related outcomes. Therefore, we aimed to analyze and compare the temporal evolution of the CORs and LOEs supporting in-hospital pharmacological and nonpharmacological recommendations for STEMI issued by the ACC, AHA, and ESC from 1990 to 2023.

Methods

The study protocol was conceived within an academic environment and was strategically framed into the principles of Project Management endorsed by the Project Management Institute (PMI).[13] The study protocol can be accessed in the Open Science Frame (OSF) platform.[14] This study is meta-research of CPGs, aimed at identifying, analyzing, and comparing the temporal evolution of both COR and LOE supporting pharmacological and nonpharmacological recommendations during the acute in-hospital management of STEMI. The procedures and data related to this research are disclosed by the corresponding author upon reasonable request, for replication of the study.

Data sources and searches

On March 18th, 2024, we searched PubMed for identifying indexed clinical guidelines from January 1990 until December 2023 published by the ACC, AHA, and ESC. The search string included controlled and noncontrolled terminologies and is shown in Supplementary Appendix 1 (pp. 7-8). Additionally, a supplementary search for relevant guidelines, corresponding to a focal and single-dated consultation on the beforementioned cardiovascular societies' online platforms as well as the immediate predecessors to any eligible shortlisted guideline, was then carried out. We also performed an exhaustive search of

reference lists of eligible guidelines, ensuring the inclusion of the highest number of records.[8-10] The systematic search and guidelines selection were performed by an experienced medical researcher, and discrepancies were solved by consultation with a senior cardiologist. Once publications were identified, they were imported onto Covidence for screening (title and abstract and sequentially full texts).

Study selection

As recommendations pertaining to STEMI management may be found in guidelines not specifically focusing on the management of ACS, we carefully evaluated guideline documents focused on coronary artery revascularization techniques (ie, percutaneous coronary intervention [PCI] and coronary artery bypass graft [CABG] surgery), management of coronary artery disease, and coronary angiography, and emergency cardiovascular care. For the eligible guidelines covering the spectrum of ACS, we excluded recommendations clearly labeled to be applicable to the management of unstable angina and Non–ST-segment Elevation Myocardial Infarction (NSTEMI or non-Q-wave myocardial infarction per old definitions), as well as those related to the management of conditions associated solely with chronic coronary syndromes. Moreover, we excluded recommendations under the category of risk stratification, physical examination, electrocardiogram monitoring, triage and transportation protocols, diagnostic cardiac biomarkers, pre and in-hospital logistic of care, as well as follow-up after the acute event. These exclusions ensure that our focus remains only on those recommendations pertinent to in-hospital STEMI management.

Data extraction and quality assessment

The definition of terminologies utilized in our study followed the endorsements by the World Health Organization (WHO), the ACC, and the AHA. The full determination of all relevant terminologies pertaining to this research (clinical guidelines, recommendations, focused updates, pharmacological interventions, nonpharmacological interventions, and acute STEMI) is available in Supplementary Appendix 2 (pp. 9-10). Eligible guidelines statements were those in which the recommendation clearly focused on an intervention intended for management of STEMI in the acute phase, dichotomized as pharmacological or nonpharmacological approaches. Listed pharmacological recommendations were framed into pharmacological subgroups (third level), according to the Anatomical Therapeutic Chemical (ATC) Classification System, controlled by the World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOCC).[15] nonpharmacological recommendations during the acute STEMI management encompassed therapies that do not essentially and entirely involve taking active chemical compounds (ie, PCI, coronary angiography, ventricular assistance devices, and intra-aortic balloon counter pulsation). As our analytical focus on clinical trials of interventions, we included only recommendations applicable to the in-hospital management of STEMI patients. Thus, we dismissed recommendations related to risk stratification, physical examination, electrocardiogram (ECG) monitoring, triage and transportation protocols, diagnostic cardiac biomarkers, pre and in-hospital logistic of care (ie, emergency medical services, public education in cardiopulmonary resuscitation, and admission to cardiac coronary unit's procedures), as well as follow-up after the acute event. The comprehensive list of pharmacological and nonpharmacological interventions considered eligible for abstraction is available in Supplementary Appendix 3 (pp. 11-20).

Data extraction was initially performed by 1 methodologist-physician, with subsequential assessment of completeness by a peer-researcher specialized in cardiovascular research. The final list of recommendations was prepared later under the supervision of a senior interventional cardiologist and collaborating with a senior epidemiologist. Any analytical or theoretical uncertainty by the primary clinicians was solved through remote or in-person discussions, as were discrepancies related to the extraction of recommendation data. Besides recording the text of each recommendation, we extracted each recommendation's COR and LOE. We did not provide any further judgment or assessment of the proposed definition displayed within the guidelines, and we utilized the same classification as originally reported by the guideline. Along with the categorization of the LOE among included guidelines, we extracted the CORs encompassing 5 levels. The full description of all 3 LOE and the 5 COR as described in Supplementary Appendix 2 (pp. 9-10).

Data synthesis and analysis

For capturing the temporal evolution of recommendations, we tabulated all extracted data from individual guideline documents in a single database. We further randomly assigned codes (identifiers) to the recommendations, using a coding system presented in detail in the Supplementary Appendix 4 (pp. 21-48). The coding system utilized principles of semantic similarity and thematic-based clusterization to identify equivalent recommendations over time. For most recommendations, we followed the clinical guidelines subheading identifiers to perform the matching of equivalent codes across the database, always maintaining the determined recommendation under this major category of original reporting. Recommendations on the various types of cardiac implantable electronic devices (eg, implantable cardioverter defibrillator, ICD) were carefully allocated under a general group (ICD), and subtypes within each category were also labeled (eg, implantable defibrillators, permanent pacing, transvenous catheter pace, tempo-

rary pacing, and temporary transvenous pacing). However, for some recommendations (such as those related to management of complications and the use of prophylactics or symptomatic drugs) we decided to assign them to a separate category based on our clinical experience. We managed the overlapping of recommendations on an equivalent code by checking the consistency among guidelines (evaluating each directly related predecessor, in the case of subsequential documents). Nevertheless, we deemed as different those recommendations from the same guideline document that were considered semantically and technically equivalent but with contrasting COR and/or LOE. To capture the temporal evolution of both pharmacological and nonpharmacological recommendations, we initially assessed the annual proportion of class-specific CORs and LOE across the database. We expressed these results as the total number (N) and percentage (%), by year and subcategory. Lastly, we compared the focal changes of LOE from 2 comparable guidelines (eg, ACC/AHA [2004/2013] and ESC [2017/2023], using the chi-square test). We reported out data graphically using heat maps, linear plotting graphs, and Sankey diagram, stressing the changes in CORs and LOEs over time. We processed and tracked all the modifications of any subcategory of recommendation at different LOEs. Two medical statisticians coordinated the mathematical assessments using R software (version 4.3.1).

Results

General findings

Our electronic search yielded 805 references (as 775 unique publications), with 136 duplicates automatically identified by our systematic review management platform. On the first stage of screening (title and abstract), we considered 567 studies as irrelevant (Supplementary Appendix 5, pp. 52-110). Throughout full text evaluation, 72 records were shortlisted, with 54 records being excluded (reasons reported in Figure 1 and Supplementary Appendix 6, pp. 111-118). With regard to our hand search, 8 additional guidelines were obtained. Therefore, our meta-research analysis collates data from 26 clinical practice guidelines (published as 49 records) issued by the selected cardiology societies, from 1990 to 2023 (1990,[16,17] 1995,[18-20] 1996,[21,22] 1999,[23,24] 1999,[25,26] 1999,[27,28] 2000,[29] 2001,[30,31] 2003,[32,33] 2003,[34,35] 2004,[36,37] 2005,[38] 2005,[39] 2008,[40,41] 2008,[42] 2009,[43-45] 2011,[46-48] 2013,[49,50] 2014,[51,52] 2015,[53-55] 2016,[56,57] 2016,[58,59] 2017,[60] 2017,[61] 2021,[62,63] 2023[64]), as showed in Table 1. Guidelines were predominantly published in the Journal of the American College of Cardiology ($n = 18$), Circulation ($n = 18$), and European Heart Journal ($n = 5$). Although mostly endorsed by the ACC, AHA, or the ESC, some included guidelines had endorsement approval from other medical organizations, including the Society for Cardiovascular Angiography and Interventions (SCAI)[53,56-58,62,63] and the American Association for Thoracic Surgery (AATS).[56-58]

Chronological assessment of CORs and LOE, 1990-2023

Our historical registration of recommendations from 1990 to 2023 encompasses 2,139 recommendations across 26 guidelines. Table 2 depicts the annual total number of recommendations and their associated LOEs and CORs for the 3 selected cardiology societies. Guidelines covered specific topics or were focused updates (eg, PCI,[30,39,39,47,53,55] coronary artery revascularization strategies,[51,57,57,62] and dual antiplatelet therapy[58,60]) or were presented as an overarching guidelines (on both ACS, acute myocardial infarction, and STEMI[16,22,24,29,34-36,40,49,61,64]). For the 33 years evaluated, the LOE fluctuated across the years, with the highest proportion of high LOE (LOE-A) registered in 1999 and 2021. Figure 2 shows the general evolution of the LOE (Figure 2A) and COR (Figure 2B) throughout the tracked period. After analyzing the dataset to determine if a significant change over the years occurred, we observed a constant fluctuation in the number of recommendations under an assigned high, moderate, and low LOE (significant change in the proportion among the LOEs over the years ($\chi^2 = 114.65$, P-value $< .01$). Despite presenting the distribution of LOE across included guidelines through proportion visualization, we acknowledge the fact that they may obscure the absolute increase in LOE-A recommendations in case the total number of recommendations concomitantly grows. Thus, we are also presenting absolute counts and proportions to provide a more balanced view of tendencies across the time (Table 2).

Figure 3 illustrates the proportions (as %) of different LOE across the multiple COR. The heatmap suggests that Class I recommendations have a relatively low number of high-quality evidence. Considering all included recommendations, we observed that approximately 70% of highly advised clinical recommendations are based on either moderate (37.3%) or low-quality evidence (32.6%). Similarly, Class II-a and Class II-b recommendations were shown to have a stronger reliance on lower-quality evidence, precisely 45.9% and 49.3%, respectively. As far as Class III recommendations are concerned, they predominantly relied on moderate-quality evidence (proportion of 45.1%). We further evaluated the variation and concentration of different LOE over the years for different pharmacological and nonpharmacological categories. Figures 4A, 4B, and 4C (Supplementary Appendix 7, pp. 120-122) show the temporal evolution of the LOE among all categorized pharmacological interventions (LOE-A, LOE-B, and LOE-C, respectively) while in Figures 5A, 5B, and 5C (Supplementary Appendix 7, pp. 123-125) we report the different LOE among all nonpharmacological interventions. There was substantial variability by year in COR

Figure 1. Review flowchart diagram.

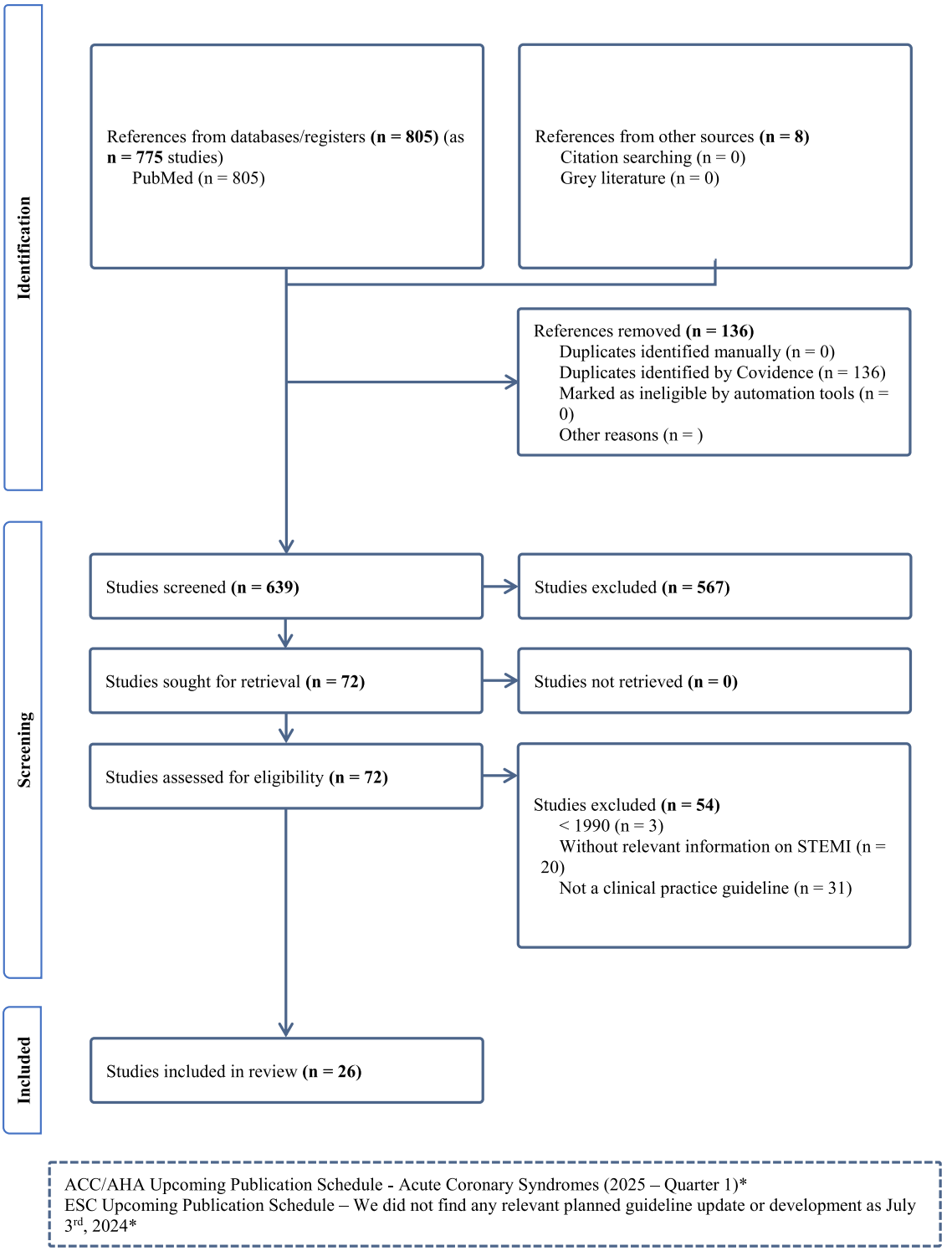


Table 1. Summary of included clinical practice guidelines, 1990-2023.

Reference ID	Year	Main focus	Publications generated
Gunnar *et. al*	1990[25,26]	Acute Myocardial Infarction	Circulation and Journal of the American College of Cardiology
Ritchie *et. al*	1995[27–29]	Cardiac Radionuclide Imaging	Circulation, Journal of the American College of Cardiology, and J of Nuclear Cardiology
Ryan *et. al*	1996[30,31]	Acute Myocardial Infarction	Circulation and Journal of the American College of Cardiology
Ryan *et. al*	1999[32,33]	Acute Myocardial Infarction	Circulation and Journal of the American College of Cardiology
Scanlon *et. al*	1999[34,35]	Coronary Angiography	Circulation and Journal of the American College of Cardiology
Eagle *et. al*	1999[36,37]	Coronary Artery Bypass Graft Surgery	Circulation and Journal of the American College of Cardiology
AHA 2000*	2000[38]	Reperfusion Techniques	Circulation
Smith *et. al*	2001[39,40]	Percutaneous Coronary Intervention	Circulation and Journal of the American College of Cardiology
Klocke *et. al*	2003[41,42]	Cardiac Radionuclide Imaging	Circulation and Journal of the American College of Cardiology
Van de Werf *et. al*	2003[43,44]	Acute Myocardial Infarction/STEMI	Circulation and Journal of the American College of Cardiology
Antman *et. al*	2004[45,46]	Acute Myocardial Infarction/STEMI	Circulation and Journal of the American College of Cardiology
Hesse *et. al*	2005[47]	Myocardial Perfusion Imaging	European Journal of Nuclear Medicine and Molecular Imaging
Silber *et. al*	2005[48]	Percutaneous Coronary Intervention	European Heart Journal
Antman *et. al*	2008[49,50]	Acute Myocardial Infarction/STEMI	Circulation and Journal of the American College of Cardiology
Hesse *et. al*	2008[51]	Cardiac Radionuclide Imaging	European Journal of Nuclear Medicine and Molecular Imaging
Kushner *et. al*	2009[52–54]	Acute Myocardial Infarction/STEMI	Circulation, Journal of the American College of Cardiology, and Catheter Cardiovascular Interventions
King *et. al*	2011[55–57]	Percutaneous Coronary Intervention	Circulation, Journal of the American College of Cardiology, and Catheter Cardiovascular Interventions
O'Gara *et. al*	2013[58,59]	Acute Myocardial Infarction/STEMI	Circulation and Journal of the American College of Cardiology
Windecker *et. al*	2014[60,61]	Myocardial Revascularization	European Heart Journal and European Journal of Cardio-Thoracic Surgery
Levine *et. al*	2015[62–64]	Percutaneous Coronary Intervention	Circulation, Journal of the American College of Cardiology, and Catheter Cardiovascular Interventions
Patel *et. al*	2016[65,66]	Coronary Revascularization	Journal of Nuclear Cardiology and Journal of the American College of Cardiology
Levine *et. al*	2016[67,68]	Dual Antiplatelet Therapy	Circulation and Journal of the American College of Cardiology
Valgimigli *et. al*	2017[69]	Dual Antiplatelet Therapy	European Heart Journal
Ibanez *et. al*	2017[70]	Acute Myocardial Infarction/STEMI	European Heart Journal
Lawton *et. al*	2021[71,72]	Coronary Artery Revascularization	Circulation and Journal of the American College of Cardiology
Byrne *et. al*	2023[73]	Acute Myocardial Infarction/STEMI	European Heart Journal

*Not indexed under any specific author – Listed under the "The American Heart Association in collaboration with the International Liaison Committee on Resuscitation".

and LOE across different pharmacological and nonpharmacological classes.

The ACC/AHA, and ESC started to systematically report the LOE for each recommendation within their clinical practice guidelines after 2001 and 2003, respectively. With regards to the ACC/AHA guidelines, from 2001 to 2021, most recommendations were based on both LOE-B (n = 360; 45.6%) and LOE-C (n = 309; 39.2%), with only 15.1% of recommendations being classified as LOE-A (n = *119*). Similarly, the ESC evidenced a slightly similar pattern, with most recommendations based on low LOE (n = 319; 37.7%) and moderate LOE (n = 293, 32.9%), and a smaller percentage of recommendations based on high LOE (n = 278; 32.8%). To note, our assessment comparing the LOE between the ACC/AHA and the ESC revealed a statistically significant difference in the distribution of LOE across the 3 cardiology societies (χ^2 = 54.118, df = 4, P-value < 0.001). The generated Sankey diagram (Figure 6, Supplementary Appendix 7, pp. 123) illustrates the temporal changes in the LOEs

Table 2. Annual distribution of classes of recommendations (CORs) and level of evidence (LOE) among included guidelines from the AHA, ACC, or ESC.

Year	Level of evidence			Class of recommendation				Total (%)	Cardiology society
	A*	B†	C‡	I§	IIa‖	IIb¶	III**		
1990	0	0	0	51	41	15	28	135	ACC/AHA
1995	0	0	0	1	1	0	0	2	ACC/AHA
1996	0	0	0	79	36	32	35	182	ACC/AHA
1999	2	1	0	81	39	35	28	183	ACC/AHA
2000	0	0	0	1	5	0	0	7	ESC
2001	3	18	25	9	16	9	12	46	ACC/AHA
2003	16	18	4	22	9	3	4	38	ACC/AHA–ESC
2004	52	136	153	197	69	27	48	341	ACC/AHA
2005	6	15	14	19	8	5	3	35	ACC/AHA–ESC
2008	46	116	98	152	59	31	18	260	ACC/AHA–ESC
2009	5	18	12	18	10	5	2	35	ACC/AHA
2011	3	19	10	10	13	6	3	32	ACC/AHA
2013	15	66	32	68	24	13	8	113	ACC/AHA
2014	43	56	68	78	65	21	3	167	ACC/AHA–ESC
2015	1	1	1	0	0	2	1	3	ACC/AHA
2016	7	14	10	14	7	8	2	31	ACC/AHA
2017	67	68	78	107	56	28	22	213	ESC
2018	39	35	59	73	31	14	15	133	ESC
2021	8	7	1	4	3	6	3	16	ACC/AHA
2023	54	50	63	80	43	27	17	167	ESC
Total	367	638	628	1064	535	287	252	2139	

* LOE-A associates with high-quality evidence from more than 1 randomized clinical trials (RCTs), meta-analyses of high-quality RCTs, or one or more RCTs corroborated by high-quality registry studies.

† LOE-B associates with moderate-quality evidence from 1 or more RCTs, meta-analyses of moderate-quality RCTs.

‡ LOE-C associates with randomized or nonrandomized observational or registry studies with limitations of design or execution or the meta-analyses of such studies, physiological or mechanistic studies in human subjects, or consensus of expert opinion based on clinical experience.

§ Suggested phrases for writing recommendations: (1) Is recommended (2) Is either indicated, useful, effective, beneficial (3) Should be performed or administered (4) Comparative Effectiveness Phrases*—The treatment of the strategy is recommended or indicated in preference to treatment B (5) The treatment should be chosen over treatment B.

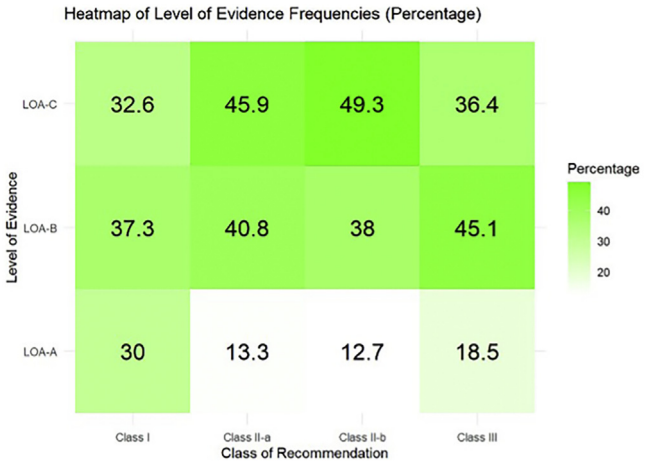
‖ Suggested phrases for writing recommendations: (1) Is reasonable (2) Can either be useful, effective, or beneficial; (3) Comparative-Effectiveness Phrases—The treatment or the strategy A is probably recommended or indicated in preference to treatment B or it is reasonable to choose treatment A over treatment B.

¶ Suggested phrases for writing recommendations: (1) May or might be reasonable (2) May, might be considered (3) Usefulness or effectiveness is either unknown, unclear, uncertain, or not well established.

** Suggested phrases for writing recommendations: (1) Is not recommended (2) It produces harm - Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

Figure 2. Trends in LOE (A) and COR (B) in STEMI-related guidelines (1999-2023).

Figure 3. Cross-tabulation ofLOE and COR in STEMI-related guidelines (1999-2023).



of included recommendations from multiple years, suggesting major patterns. Recommendations from earlier years (ie, 2004 and 2008), are predominantly under a moderate- and low-quality of evidence. Additionally, we observe the persistence of recommendations classified as LOE-C across different years, stressing the recurring trend of recommendations with low-quality of evidence. Lastly, it is observed a high variability in the strength of evidence underpinning included recommendations over time.

Comparative temporal analysis of pharmacological and nonpharmacological interventions, 1990-2023

The sub categorical assessment evidenced that pharmacological interventions presented a slightly higher proportion of recommendations under the high LOE (21.5%), compared to nonpharmacological interventions (13.8%), *P*-value < 0.01. nonpharmacological interventions have shown to have slightly higher proportion of recommendations under a low LOE compared to pharmacological interventions (30.4% vs 29.4%, *P*-value $<$ .05). To note, both types of cardiovascular-related interventions predominantly were associated with Class I recommendations, in which nonpharmacological interventions presenting a greater proportion of recommendations under this category compared to pharmacological interventions (73.5% vs 68.8%). Interestingly, nonpharmacological recommendations presented a slightly larger proportion of Class III recommendations (9.9%) compared to pharmacological interventions (7.1%). Our statistical analysis also suggested that significant changes in pharmacological versus nonpharmacological recommendations occurred over time ($\chi^2 = 267.25$, *P*-value < 0.05), as well as in the subareas within each type of recommendations (pharmacological subareas yielded a $\chi^2 = 1{,}159.5$; *P*-value < 0.05, while nonpharmacological subareas yielded a $\chi^2 = 1{,}592.16$; *P*-value < 0.05). The full list of all subcategories of pharmacological and nonpharmacological interventions included in our analysis is presented in Tables 3 and 4. Due to space limitations in the main publication, we included additional findings summarization in Supplementary Appendix 7 (pp. 119-125).

Focal guideline evolution - ACC/AHA (2013 vs 2004) and ESC (2023 vs 2017) comparative analysis

The focal comparison of 2 consecutive guidelines by the ACC/AHA and ESC was performed to evaluate the proportion of recommendations that were directly modified over the years (either having an upgrade or downgrade of both COR and LOE). Table 5 shows the numbers of recommendations per guidelines in each assessed category. Considering the ACC/AHA guidelines, in the updated 2013 version, a smaller proportion of recommendations based on LOE-A was observed compared to 2004 (13.3% vs 15.2%, *P*-value < 0.05). On the other hand, a higher proportion of recommendations under the LOE-B was observed in 2013 (58.4%) compared to 2004 (39.9%). To note, a decrease in the proportion of recommendations classified as LOE-C was noticed in 2013 (28.3%) compared to 2004 (44.9%). When assessed the recommendations that were particularly changed in the 2013 update, we observed that 13 unique recommendations were changed (list of changed recommendations presented in the Supplementary Appendix 8, pp. 126-129). As far as the ESC is concerned, a steady proportion of recommendations classified under different LOEs were noticed from 2017 to 2023. Particularly, 4 unique recommendations were directly changed (list of changed recommendations presented in Supplementary Appendix 9 (pp. 129).

Table 3. Distribution of the level of evidence (LOE) and class of recommendation (COR) of pharmacological interventions, by subcategory.

Subcategory of pharmacological interventions	Pharmacological COR				Pharmacological LOE		
	I	II-a	II-b	III	A	B	C
Agents acting on the renin-angiotensin-system (C09)	18	9	0	1	24	4	0
Aldosterone antagonists and other potassium-sparing agents (Mineralocorticoid receptor antagonist, C03D)	13	0	0	0	6	7	0
Analgesic (N02), other analgesics and antipyretics (N02B), or ant-inflammatory agents (S01B)	8	4	6	5	0	4	15
Angiotensin II receptor blockers (ARBs), Plain (C09C)	17	7	3	0	4	10	3
Antiarrhythmic drugs - C01B	19	10	10	20	2	13	24
Anticholinergic agents	20	3	6	10	0	0	2
Beta blocker agents - C07	54	14	6	11	23	19	12
Calcium channel blockers (C08)	3	7	3	11	3	4	5
Cardiac stimulants (positive chronotropic, ionotropic, and dromotropic agents) (C01C)	7	2	6	0	0	4	11
Corticoids (S02B)	0	0	3	0	0	1	0
Digitalis glycosides (C01AA)	4	1	2	2	2	2	3
Diuretics (C03)	0	0	5	0	0	0	5
Dual anti-Platelet	72	33	29	7	45	58	38
Full anticoagulation	92	55	14	13	30	48	63
GP IIb/IIIa inhibitors	2	19	8	2	5	17	8
Lipid modifying agents (C10)	31	13	5	0	18	15	4
Magnesium	0	6	2	3	3	2	6
Miscellaneous	2	3	4	3	2	5	5
Oxygen (All other therapeutical products, V03A)	20	3	2	4	1	4	16
Plant alkaloids and other natural products (L01C)	0	1	2	0	2	1	0
Platelet aggregation inhibitors (excluding heparin) (B01AC)—single antiplatelet	88	21	20	5	27	49	43
Prophylactics and symptomatic	11	10	2	0	6	9	8
Psychotropic or anxiolytics	1	6	3	0	0	2	6
Sex hormones and modulators of the genital system (G03) / Hormone replacement therapy	0	0	2	0	1	1	0
Thrombolytic or fibrinolytic therapy	34	21	8	12	18	21	7
Triple antithrombotic therapy	2	8	2	5	1	4	12
Vaccines (J07)	3	0	0	0	1	2	0
Vasodilators used in cardiac diseases (Nitrates)	17	3	5	6	3	5	11

Given codes were based on the Anatomical Therapeutic Chemical (ATC) Classification System maintained by the World Health Organization Collaborating Centre for Drug Statistics Methodology (WHO–CC).

Discussion

Main findings of this study

In our study, we evaluated 2,139 recommendations abstracted from STEMI-related CPGs endorsed by 3 major cardiological medical societies from 1990 to 2023. Overall, the proportion of LOE-A recommendations was only 17.1%, followed by a 59.1% based on both LOE-B or LOE-C (29.8% and 29.3%, respectively), with significant change in the LOE across the evaluated time. Additionally, 50% of recommendations were classified as Class I, while 25% were Class II-a, 13% Class II-b, and 12% Class III. Time-series assessment evidenced progressive increase in recommendations derived from randomized clinical trials (RCT) and meta-analyses, with notable peaks in 2004, 2017, and 2023. Paradoxically, reliance on strongly advocated recommendations (Class I) has escalated longitudinally over the years. Pharmacological interventions had historically higher LOEs (21.5%) compared to nonpharmacological therapies (13.8%). Prevailing pharmacological interventions comprised anticoagulants and dual antiplatelets, whilst nonpharmacological interventions chiefly embraced PCI and ICDs. Sequential guidelines analyses (2004/2013 [ACC/AHA] and 2017/2023 [ESC]) suggested minimal variation in the LOEs/CORs of recommendations. In other words, despite 3 decades of scientific and technological efforts, the evidence basis landscaping STEMI-related guideline recommendations has progressed far more slowly, suggesting a chronic misalignment between clinical advancement and the strength of underlying evidence. To the best of our knowledge, our research stands as the first pathology-specific, intervention-stratified, prospective temporal monitoring meta-research evaluating the coevolution of guidelines underpinning acute management of STEMI and their supporting evidence as 2 dynamically cointeractive systems. Additionally, using principles related to thematic and content analyses, we developed a semantic and lexical coding system to quanti-

Table 4. Distribution of the level of evidence (LOE) and class of recommendation (COR) of nonpharmacological interventions, by subcategory.

Subcategory of nonpharmacological interventions	Nonpharmacological COR				Nonpharmacological LOE		
	I	II-a	II-b	III	A	B	C
Absolute bed rest	0	1	0	1	0	0	2
Angioplasty	4	6	6	10	0	0	1
Arterial pressure monitoring	14	15	6	6	1	1	20
Balloon flotation right heart catheter monitoring	9	5	1	3	0	0	0
Cardiac implantable electronic devices	52	25	16	24	5	6	22
Coronary angiography	27	12	5	5	10	11	7
Diagnosis | Exercise testing	2	0	1	3	0	2	4
Diet	15	6	2	0	4	17	2
Emergency or urgent coronary bypass surgery	51	26	11	10	8	33	19
Imaging	44	37	14	9	6	25	66
Implantable ventricular assist devices	4	2	3	4	0	10	2
Intra-aortic balloon counterpulsation and other circulatory assist devices	22	13	11	6	1	13	12
Intracoronary physiologic measurements	0	1	2	1	0	1	3
Invasive evaluation	3	0	0	0	0	3	0
Management of complications approaches	46	15	5	3	6	16	35
Noninvasive evaluation of low-risk patients	7	0	4	4	0	1	2
Percutaneous coronary intervention	153	89	41	39	81	140	95
Psychological support	1	2	0	0	1	0	2
Secondary prevention (management of underlying diseases and habits)	51	6	2	0	15	33	11
Surgical corrections | approaches	12	15	6	0	2	12	19
Temperature management	4	0	0	0	0	4	0
Ultrafiltration	0	0	2	0	0	2	0

Table 5. Focal temporal comparison of 2 consecutive guidelines from the ACC/AHA and ESC.

Variable	Number of recommendations (%)			
	ACC/AHA		ESC	
	Old (2004) $n = 341$	Recent (2013) $n = 113$	Old (2017) $n = 213$	Recent (2023) $n = 167$
LOE-A* (Randomized or nonrandomized)	52 (15.2%)	15 (13.3%)	67 (31.5%)	54 (32.3%)
LOE-B* (Benefit$^{2+ \text{or } 1+}$/Risk^{1-}) (Randomized or nonrandomized)	136 (39.9%)	66 (58.4%)	68 (31.9%)	50 (30.0%)
LOE-C* (Benefit1^{+}/Risk^{1-}) (Limited data or expert opinion)	153 (44.9%)	32 (28.3%)	78 (36.6%)	63 (37.7%)
N/A	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Class I* (Benefit^{3+}/Risk^{1-})	197 (57.8%)	68 (60.2%)	107 (50.2%)	80 (47.9%)
Class II-a* (Benefit^{2+}/Risk^{1-})	69 (20.2%)	24 (21.2%)	56 (26.3%)	43 (25.7%)
Class II-b* (Benefit^{1+}/Risk^{1-})	27 (7.9%)	13 (11.5%)	28 (13.2%)	27 (16.2%)
Class III* (Benefit^{1-}/Risk^{1-})	48 (14.1%)	8 (7.1%)	22 (10.3%)	17 (10.2%)
N/A	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

p-value < 0.05.

tatively and objectively match, whenever applicable, recommendations across successive CPGs. These findings raise timely questions about the evolving landscape of evidence generation in acute cardiovascular care.

Context within prior evidence

Our results corroborate with several published studies that assessed the LOE and COR within clinical practice guidelines in multiple medical specialties.[9-11,65,66] For instance, Fanaroff et al.[10] suggested that only 15% of recommendations among the analyzed guidelines (from 2008 to 2018) were supported by high-level of evidence. They also stressed that after over a decade since the publication of the first large meta-research on guidelines in Cardiology (Tricoci et al.[9]) there had not been registered among guidelines a significant increase in the proportion of recommendations based on high LOE. More recently, Milbradt et al.[67] further scrutinized ESC guidelines, re-

inforcing the reliance on lower grade evidence. Similar findings were seen in other specialties. Despite our primary focus on ACS recommendations, we also observed no no substantial improvement in the LOE across the years. The observed steady tendency in the proportion of recommendation derived from limited-leveled evidence brings attention to potential barriers that limit the establishment of a scientific environment that promotes the generation of high-quality evidence for several clinical topics. Combined, this body of evidence—including our own—challenges reasonable assumption that recurrent guidelines update naturally absorb with growing intensity stronger evidence—a model not evidenced by 33 years of STEMI-related guideline development. Instead of simply framing knowledge gaps, our data reflect an important misalignment between "*types of questions clinicians most urgently require answer*" and "*the questions that existing research ecosystem is systematically incentivized to explore.*"

Some structural and methodological contributors to evidence stagnation in STEMI care

An important factor that might limit the development of CPGs based on high LOE references is the lack of high-quality clinical trials in several fields of cardiology, alongside with funding limitations for trial designs. Several systematic reviews and meta-research studies have suggested that a considerable amount of published clinical trials lack essential features of clinical usefulness (ie, including those relating to problem base, context placement, knowledge gain, pragmatism, patient centeredness, cost-effectiveness, feasibility, and transparency), and tend to emphasize the isolated effect of the intervention on a highly selected population, rather than on a group that represents clinical practice.[68-71] Additionally, several clinically relevant research questions considered in guidelines might either not have yet been addressed through high-quality investigations or are not easily amenable to standard clinical trial designs, requiring specific approaches, such as registry-based or pragmatic multicenter trials.

The current stagnation in high-quality evidence recommendations may also be resulted, at least in part, from the inherent challenges in applying traditional clinical trials designs to certain high-impact clinical questions which are often constrained by ethical considerations, limitations in achieving clinical consensus, economic limitations, and substantial patient heterogeneity. For instance, patients undergoing high-risk PCI (eg, patients with severe left ventricular dysfunction, cardiogenic shock, or with previous coronary artery bypass grafting) would benefit from the use of different mechanical circulatory support devices (such as intra-aortic balloon pumps).[72-75] However, due to ethical limitations, variability of incoming patients' conditions, and fast-paced technological development of new devices, the development of a robust, high-quality clinical trial is challenging, expensive, and time-consuming. Likewise, regulatory and economic factors might modulate the prioritization of research development, ultimately affecting the inclusion of robust evidence within guidelines.[76] In that regard, a relevant factor is the pressure from medical companies, whose funding is often directed towards novel, marketable and highly profit margin-oriented interventions rather than pragmatic evaluation of standard care or legacy therapies, while public or governmental funding remains insufficient to address many pressing care delivery or comparative-effectiveness questions.[77] This phenomenon precipitates the settlement of an evidence-generation system driven by regulatory approval as opposed to advancing guideline robustness, consistently deprioritizing clinically relevant areas but commercially unprofitable domains. Finally, even with the evidence showing benefits of a certain therapy, the translation of the findings into clinical practice depends on local healthcare funding, limiting further assessments of the interventions in registry-based RCTs. Therefore, we highlight that the scarcity of LOE-A is not a failure of guidelines committees but a manifestation of long-standing systemic disjunction between research incentives and real-world clinical need.

Our categorical comparison suggested that pharmacological interventions have a slightly higher proportion of recommendations based on LOE-A compared to non-pharmacological interventions. These findings are somewhat expected, as one might anticipate a lower LOE for nonpharmacological interventions because of the variability in incoming funding resources and the complexity of performing large-scaled and high-quality RCTs in these areas, involving multiple devices, frequently updated, and under constant technical development. Nevertheless, this finding could be potentially influenced by a particular PICO (Population, Intervention, Comparator, Outcome) research question explored among the guidelines, where nonpharmacological interventions (such as cardiac implantable electronic devices, implantable ventricular assistance devices, stents, endoprostheses, or noninvasive monitoring devices) may have been already assessed in well-funded, large, and multicenter clinical trials.[78,79] Device companies often conduct large, multicentered, RCTs, leading to higher LOE. There is a current trend, however, towards a superselection of patients through rigorous inclusion criteria, instead of pragmatic designs, limiting the generalization even of such results and the translation into changes of clinical practice. Conversely, relevant clinical research questions correlated to less invested areas in cardiology, might be affected with monetary shortage and lack of funding, ultimately reducing the number of clinical trials and consequently the overall quality of evidence. In this scenario, we may cite that many clinically essential research questions—quality-of-care metrics, systems of care and health infras-

tructural improvement, rehabilitation, and logistical optimization of care—remain underfunded or understudied, creating what can be metaphorically name as "neglected healthcare dimensions." Consequently, areas that most profoundly influence survival and equity across settings are regularly those with the weakest evidence base, not due to any inferiority in significance, but because they are less profitable.

Re-envisioning an evidence ecosystem for acute STEMI and cardiovascular care

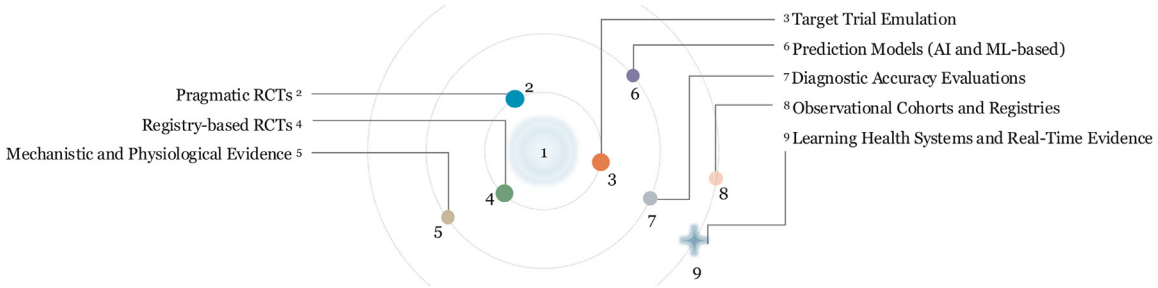
As observed among included guidelines, the ACC, AHA, and ESC apply the COR and LOE systems to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care, which is seen as a complex and difficult to be translated into daily medical practice. For example, the existing nuances between Class II-a and Class II-b are frequently confusing to healthcare providers and consumers that are looking for rapid but accurate medical information and knowledge at the point of care. In addition, recommendations are commonly affected by the subjectivity of expert opinion, introducing inconsistency and heterogeneity as experts might interpret the obtained evidence differently. We bring attention to the fact that several epidemiologically and clinically relevant questions are not commonly answered by RCTs, despite the critical importance of other types of study designs that my adequately answer these clinical questions, such as population-based cohorts, large registries and ecological/epidemiological studies. The chronic belief that all clinically important question must be answered through an RCT has inadvertently circumscribed the scope of acceptable evidence, delaying or inhibiting progress in areas where alternative designs would be more ethical, feasible, informative, and economic.

These critical challenges and disadvantages associated with the standard classification system currently adopted by the selected societies may be partially solved by the utilization of alternative methodologies, such as the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[80,81] Additionally, with the increasing usability of high-quality routinely collected data, new frameworks (including the emulated trial framework and advanced methods for causal inference) offer promising avenues to strengthen the evidence supporting clinical practice guideline recommendations in areas where RCTs might be insufficient.

In regular hospital-based clinical practice, it is common to observe the routinization associated with the delivery of certain medical interventions and therapies, based on long-term common practice. During in-hospital acute management of STEMI patients, certain "codes of conduct" are already taken in place. We observed that certain recommendations are not mentioned in CPPs indefinitely. For instance, based on the guidelines endorsed by ACC/AHA, antianginal analgesic drugs (including intravenous morphine), started to be described in detail in 1996[21,22] However, after 2008,[40,41] no further description or mention of associated recommendations has been presented among subsequent published guidelines, without adequate justification or discussion. Similarly, nitrates started to be described in 1990[16] and were last mentioned in the update of 2004.[36] The silent disappearance of some recommendations—without clearly downgrading, explicit rationale, or Class III-specific designation—hinders transparency and complicates prospective interpretation of guidelines evolution. Despite these omissions, other cardiology societies, including the Brazilian Society of Cardiology, still formulate recommendations on these therapies using limited-quality evidence.[82] Therefore, some of our results would be affected by these several routinely internalized medical practices, not adequately addressed in current guidelines. Another hypothesis for the discontinuation of certain recommendations is that they may no longer be commonly used nowadays or may have been linked to potential risks or harms. However, if this rationale is correct, the formulation of a discouraging recommendation should be explicitly labeled as Class III ("*should not be performed*"). In this perspective, their previous presence in guidelines reflect historical practices rather than ongoing clinical routines, emphasizing the evolving nature of medical standards and the importance of regularly updating guideline content to mirror current evidence and practice patterns.

We observe a statistically significant variation in the distribution of LOE categories among the ACC/AHA and the ESC guidelines, which could potentially reflect core differences in the way each society approaches clinical practice guidelines development. Both organizations operate under completely different healthcare systems (ie, funding and financial models, healthcare access and coverage, health-related costs of care, differential focus on preventive versus curative care, and role of the private sector), sociocultural expectations, and healthcare systems challenges, which may affect and structure how evidence is created and weighted. The observed contrast between the analyzed societies may be utilized and translated into practice, particularly for clinicians and practitioners who frequently rely on guidelines for decision-making. Given the potential influence in the LOE in a recommendation's efficacy and safety, variance between ACC/AHA and ESC documents might generate inconsistencies in treatment practices globally. For instance, cardiologists and specialists in cardiovascular care practicing in European-related regions might be under stronger endorsements for determined interventions under lower or higher evidence levels than in regions where the ACC/AHA guidelines are valid, leading to high variability in care practices, potentially affecting patient outcomes and global estimates for cardiovascular-related dis-

Figure 4. The evidence universe model - a dynamic, question-based structure for clinical inference.



eases and conditions. Although we could not examine the reasons for the observed heterogeneity in LOE across evaluated recommendations, further actions towards a more harmonized development of cardiology-related evidence might be timely and relevant, based on a collective and synergic collaboration within societies, minimizing variability and improving the clarity of clinical guidance worldwide.

The Evidence Universe Model: A dynamic framework for question-based assessment

As stressed in our previous sections, the development of recommendations for acute STEMI care has several structural limitations, underpinning the ways in which evidence is designed, prioritized, and ultimately translated into routine clinical practice. The long-standing assumption that all clinical questions should be amenable to RCTs overlooks the wider epistemological landscape and the need for conceptual models that more accurately capture how different study designs shape clinical inference. To respond to this gap, we propose a new question-driven framework thar reestablishes evidence not as a rigid stratified hierarchy, but as a dynamic multidimensional process, as shown in Figure 4. Traditional classification systems are following assumptions that study design grants evidentiary superiority, that RCTs solely establish causal truth, besides that evidence accumulates linearly towards meta-analytical approaches. However, we recognize that the empirical value from any given design is intrinsically conditioned on the inferential demands imposed by the clinical question under evaluation. Each study design should be seen as occupying an "orbital trajectory" defined by its fit-for-purpose attributes as opposed to traditional values and norms of methodological prestige. Compelling examples are pragmatic randomized or registry-based randomized trials as well as target trials emulations which orbits on the innermost circle when answering therapeutic causal-consequence questions, while large-, well-designed observational trials may better reside in proximal orbits when core enquiries involve rare outcomes or unethically untastable experiments. Similarly, diagnostic accuracy tests are better located to subsidize early-rule-in diagnostic decisions, whereas mechanistic (basic science studies) generates deeper insights when biological plausibility is fundamental.

The proposed Evidence Universe Model should be seen as a flexible approach—the geometry of evidence is not fixed but it reorganizes itself in accordance with the epistemic demand of the research question. The static rationale that "one-design-fits-all" is incompatible with this framework and only designs that are congruent with inferential requirements of the question are considered valid. Thus, the proposed model offers a more realistic picture of how evidence is generated, interpreted, and summarized, specially in the context of fast-paced evolving acute STEMI practice. Additionally, our model naturally integrates emerging methodological paradigms in evidence development, including real-world data analytics, causal inference methods, registry-based RCTs, and so forth. By changing the analytical focus from design hierarchy to design-question congruence, our model may improve transparency, harmonization, and methodological coherence in upcoming guidelines development process.

Strengths and limitations

Our study is based on relevant strengths. It followed a rigorous methodological framework, with clear definitions and inclusion criteria, besides a robust data management (performed by at least 2 independent investigators). Likewise, we utilized a long-term follow up, capturing a broad evolution of recommendations. However, we acknowledge some limitations. Firstly, we may have been affected (although inherently and unavoidably) by judgment bias of the LOE and CORs of recommendations from the original authors of included CPGs, without a review of the recommendations by an independent group, for comparison. This "carried-out bias" might have influenced some of our findings, which we highlighted in our discussion of the results. Additionally, the focus on acute in-hospital STEMI management recommendations emerges as another limitation, as findings may not be

similar in other diseases and conditions, even within the scope of acute and chronic coronary syndromes.

Conclusions and implications

In conclusion, acute in-hospital STEMI management guidelines from leading societies have largely relied on low to moderate LOE, and despite recurrent updates, the overall evidence quality has not markedly improved. This persistent pattern suggests a foundational challenge in cardiovascular evidence establishment—several clinically relevant research questions remain untested in strong and well-designed pragmatic clinical trials, alongside that existing RCTs commonly include bias selected individuals, limiting generalizability to real-world STEMI management. Additionally, for decades, guideline committees have relied on a classification model that is facilitative, reliable and familiar, yet far from the exemplar of transparency and methodological rigor that CPGs require. The system is still usable—like outdated operation systems—but it is progressively becoming misaligned with demands of routine and contemporary evidence synthesis field. Resolving existing challenges will need more than a pivotal standalone clinical study or purpose-built analytic model. One reasonable evidence-derived pipeline spans pragmatic designs, incorporating randomization within clinical registries, and fostering the development of real-time learning health systems that continuously incorporate practice and evidence. If implemented, these governance pathways could finally match the paces—the evidence generation and clinical practice—shifting CPG development towards a level that even the most rigor-anchored scientist would find limited basis on which to dispute.

Data sharing

We included all utilized datasets and analytical codes in our online repository webpage on Open Science Frame (DOI 10.17605/OSF.IO/BRD58).

Ethical approval

As this study did not involve any human data, ethics approval was not required.

Dissemination to participants and related patient and public communities

The present submission did not involve study participants (patients). This research was shared through conference presentations (primary conference presentation planned to occur at the American Heart Association Scientific Sessions 2024, Chicago, Illnois, March 31st, 2025) and was shared with relevant stakeholder groups, such as the American Heart Association, American College of Cardiology, and European Society of Cardiology.

CRediT authorship contribution statement

Israel Júnior Borges do Nascimento: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Renato D. Lopes:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis. **Marcos Venicius Malveira De Lima:** Methodology, Formal analysis, Data curation. **Matheus de Freitas Itaborahy:** Visualization, Formal analysis, Data curation. **Alexander C. Fanaroff:** Writing – original draft, Visualization, Validation, Formal analysis. **Brijesh Sathian:** Writing – original draft, Visualization, Validation. **Holger Thiele:** Writing – original draft, Visualization, Validation, Methodology. **Bruno Ramos Nascimento:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2025.107326.

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