

ORIGINAL RESEARCH

Accelerated Diagnostic Pathways for Suspected Acute Coronary Syndrome in Practice



A Randomized Trial of 0/1-Hour vs 0/3-Hour Troponin Testing

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ABSTRACT

BACKGROUND For suspected acute coronary syndrome (ACS), guidelines recommend using high-sensitivity troponins (hs-cTn) in accelerated diagnostic pathways (ADPs) with 0/1-hour recommended over 0/3-hour ADP. However, implementation of these ADPs, with universal use of hs-cTns, has not been directly compared in randomized trials

OBJECTIVES This study sought to compare the efficiency and safety of the European Society of Cardiology (ESC) 0/1-hour and a 0/3-hour ADP when implemented in real-world clinical practice.

METHODS This pragmatic, randomized, noninferiority implementation trial compared the safety and efficiency of clinician decision making using these 2 pathways. To prevent incorporation bias, an independent hs-cTnI was used for formal adjudication using the fourth universal definition of myocardial infarction (MI). Efficiency was judged by the proportion of patients discharged within 4 hours. The safety endpoint was major adverse cardiac events (MACE) within 30 days (adjudicated index or representation type 1 MI, cardiovascular death, and urgent coronary revascularization) for those who were considered not to have ACS and discharged. The noninferiority margin, for absolute difference in sensitivity, between the ESC 0/1-hour and the 0/3-hour ADP was set at 3%, assessed with a 1-sided 97.5% CI.

RESULTS From December 2021 to July 2024, of 13,983 screened 3,543 individual patients with suspected ACS were recruited and consented from 2 major emergency departments in North-West England, with 100% follow-up achieved for all representations to any national hospital. The median age was 60 years (IQR: 49.5-70.5 years), 53% were men, 6.7%, and 7.6% had adjudicated index type 1 MI and MACE within 30 days, respectively. The turnaround time from sample to result for central laboratory hs-cTnT was 81 minutes (IQR: 69-101 minutes). The proportion of patients discharged within 4 hours was relatively low and did not differ substantially (21.8% vs 19.2%, $P = 0.07$). In addition, the 0/1-hour pathway was noninferior for safety, in patients discharged, compared with the 0/3-hour pathway, absolute difference in sensitivity was +4.2% (1-sided 97.5% CI: -2.5) in favor of the 0/1-hour pathway. The calculated sensitivities were 93.7% (95% CI: 88.4%-97.1%) vs 89.5% (95% CI: 82.7%-94.3%), respectively.

CONCLUSIONS Implementation of the ESC 0/1-hour pathway failed to discharge significantly more patients within 4 hours of presentation compared with the 0/3-hour ADP. In addition, The ESC 0/1-hour was noninferior to the 0/3-hour hs-cTn pathway for safety of discharge, although safety for both pathways was less than that imputed by observational studies. This trial demonstrates that perceived benefits to emergency department efficiency of a reduced sampling interval are mitigated by central laboratory turnaround times as well as system constraints. (Pragmatic Randomised Trial of the ESC 0/1 Versus 0/3 Hour Troponin Pathway [MACROS2]; [NCT05322395](https://doi.org/10.1016/j.jacc.2026.02.5135)) (JACC. 2026;88:1211-1221) © 2026 by the American College of Cardiology Foundation.

ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

ADP = accelerated diagnostic pathway

AHA = American Heart Association

ESC = European Society of Cardiology

hs-cTn = high-sensitivity troponin

Each year there are 10 million presentations with chest pain to emergency departments in Europe, with a similar incidence in the United States.^{1,2} Only 10% of patients are diagnosed with acute myocardial infarction (MI).³ Small improvements in efficiency can improve patient care and use of resources, facilitating prompt diagnosis and intervention or early discharge.

The European Society of Cardiology (ESC) adopted a class 1 recommendation for the ESC 0/1-hour accelerated diagnostic pathway (ADP) with the American College of Cardiology/American Heart Association (ACC/AHA) also recently switching to recommend repeat sampling at 1 or 2 hours.^{2,4} Evidence to support the ESC 0/1-hour ADP is abundant but mostly observational.⁵⁻¹² Observational studies apply predefined, assay-specific, clinical decision limits to a cohort of patients to determine safety and clinical utility. These criteria are then used as a surrogate marker of real-world clinical performance. However, prospective randomized comparisons of clinicians acting on different cutoffs are needed to truly understand their clinical utility.

Two randomized controlled trials (RCTs) have compared the ESC 0/1-hour ADP using hs-cTn with a 0/3-hour ADP.^{13,14} However, in the standard care arm of both trials, cTn values were either masked, to 30 ng/L, essentially rendering it not hs-cTn, or did not consistently use an hs-cTn assay. In addition, 2 prospective studies have assessed implementation of the ESC 0/1-hour ADP, either in a dedicated chest pain unit or in private health care settings.^{10,15} Therefore, to date, no randomized trial using hs-cTn in both arms has directly compared the ESC 0/1-hour ADP with the more widely adopted 0/3-hour ADP. Accordingly, we undertook such a trial.

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METHODS

STUDY DESIGN AND PARTICIPANTS. The Mersey Acute Coronary syndrome Rule-Out Study (MACROS-2;

NCT05322395) is a dual-center, randomized implementation trial undertaken in the emergency departments of 2 large university hospitals in Northwest England, with national follow-up through electronic health records. It compares both the efficiency and safety of clinician decision making using the ESC 1-hour ADP (Supplemental Figure 1) vs the ESC 3-hour ADP (Supplemental Figure 2), both using a hs-cTnT assay (Roche Elecsys Fifth Generation). The protocol for this trial has been published previously.¹⁶

This trial was approved by the local Research Ethics Committee (SP0635) and Health Research Authority and by each trial site. The trial was conducted in accordance with the declaration of Helsinki.

STUDY PARTICIPANTS. Patients were included in the study if they presented to the emergency department with chest pain within 12 hours of the onset or peak severity of symptoms that were suspicious of a cardiac cause (Supplemental Figure 3) and were aged 18 years or older.

Patients were enrolled between 0900 and 2100 from December 2021 until July 2024. Participant enrollment and the final discharge population from the emergency department and those admitted to hospital are shown in Figure 1.

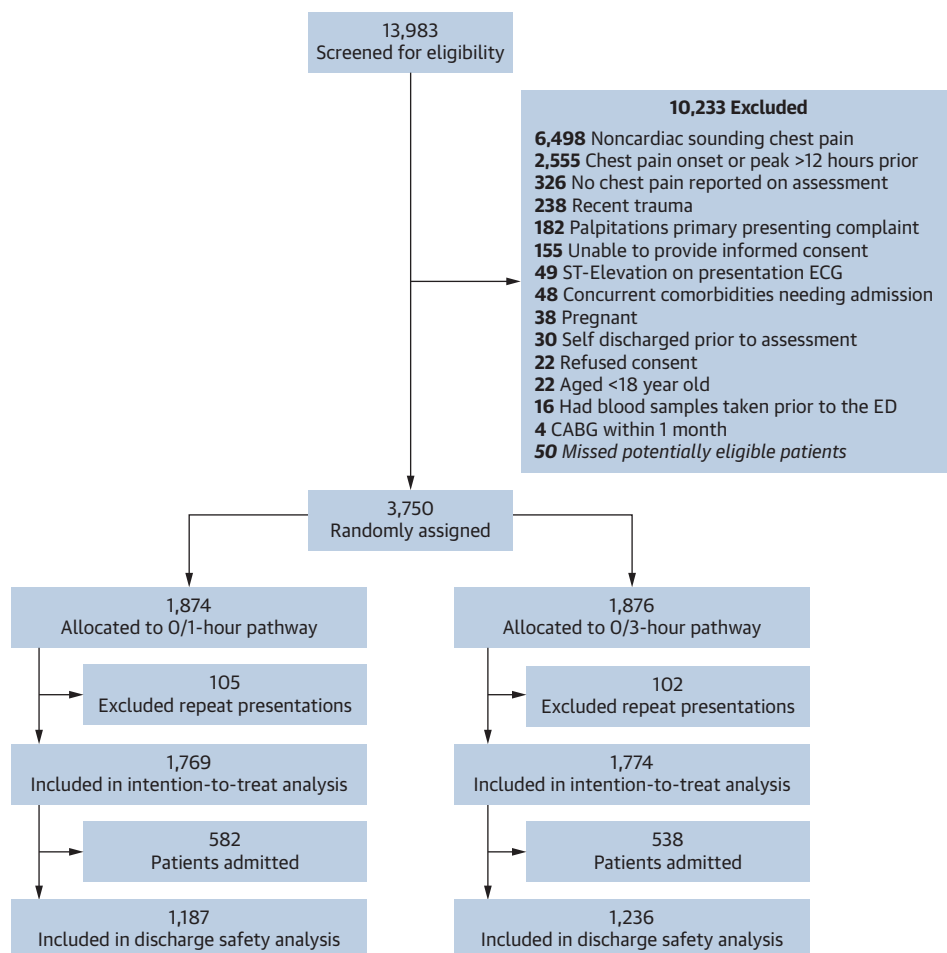
PROCEDURES. Eligible patients were consented and enrolled by research fellows and nurses based in the emergency department. Patients could be consented before or after the initial blood draw. If a patient refused consent following blood draw, all trial samples were destroyed. Patients could opt out of the trial at any time at which point their stored samples would be destroyed. Following consent there were no patients who withdrew from the study. Blood samples, both initial and follow-up in both arms, were taken by the research team for hs-cTnT (Roche Elecsys), hs-cTnI (Abbott Alinity) and any other laboratory tests requested by the emergency department clinicians.

A pathway breach was defined as any patient, whose ADP triage recommendation did not rule out

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

FIGURE 1 CONSORT Diagram Detailing the Screening and Randomization of Participants



MI but who was discharged by their clinician or conversely if recommendation was discharge but the patient was admitted. The hs-cTnT assay used for clinical decision making in both hospitals was the Roche Elecsys hs-cTnT assay performed on the cobas e601 and e801 platforms. The hs-cTnI assay (Abbott Alinity), drawn from the same sample, was used in the blinded (paired consultant cardiologist adjudicators were blinded to hs-cTnT results and to their paired consultant's judgment) adjudication process for MI. The analytical performance of both assays is outlined in [Supplemental Table 1](#). The quality control of assays for both hospitals was undertaken at Liverpool clinical laboratories and is detailed in the protocol.¹⁷

OUTCOMES. The primary efficacy endpoint, to determine real-world efficiency, was the proportion of patients discharged within 4 hours of presentation to the emergency department.

The primary safety endpoint was major adverse cardiac events (MACE) within 30 days for those who were discharged. MACE was a composite endpoint consisting of type 1 MI (this included both index presentation MI [in those discharged] and representation within 30 days with adjudicated type 1 MI), urgent coronary revascularization, or cardiovascular death within 30 days of discharge.

To assess safety across the total population (and not only those discharged), we compared the rate of MACE at 30 days, excluding index type 1 MI, across both ADP arms.

Secondary outcomes included the total proportion of patients discharged by each arm, safety of discharge for index MI alone, median emergency department length of stay (LOS) for those discharged from the emergency department, the proportion of patients, and number of clinical events in those whose clinicians acted against pathway recommendations.

TABLE 1 Patient Demographics

	All (N = 3,543)	1 hour (n = 1,769)	3 hour (n = 1,774)
Nonmodifiable Risk Factors			
Median age (IQR)	60 (49.5-70.5)	60 (49.5-70.5)	60 (49.5-70.5)
Men	1,888 (53.3)	940 (53.1)	948 (53.4)
Family history IHD	1,386 (39.1)	686 (38.8)	700 (39.5)
Early presenters ^a	960 (27.1)	496 (28.0)	464 (26.2)
Modifiable Risk Factors			
Median BMI (IQR)	28.0 (24.7-31.4)	28.1 (24.6-31.5)	28.0 (24.6-31.4)
Hypertension	1,496 (42.2)	759 (42.9)	737 (41.5)
Diabetes	605 (17.1)	309 (17.5)	296 (16.7)
Hypercholesterolemia	775 (21.9)	374 (21.1)	401 (22.6)
Nonsmoker	1,555 (43.9)	747 (42.2)	808 (45.5)
Ex-smoker	1,332 (37.6)	692 (39.1)	640 (36.1)
Current smoker	656 (18.5)	330 (18.7)	326 (18.4)
Past Medical History			
Previous MI	552 (15.6)	276 (15.6)	276 (15.6)
Previous PCI	371 (10.5)	198 (11.2)	173 (9.8)
Previous CABG	132 (3.7)	60 (3.4)	72 (4.1)
Previous TIA/CVA	217 (6.1)	98 (5.6)	119 (6.7)
Known PVD	101 (2.9)	55 (3.1)	46 (2.6)
Known CAD stenosis ≥50%	246 (6.9)	120 (6.8)	126 (7.1)
Presentation ECG (n = 3,531)			
T-wave inversion	860 (24.4)	434 (24.6)	426 (24.1)
ST-depression	290 (8.2)	154 (8.8)	136 (7.7)
Normal ECG	2,589 (73.3)	1,281 (72.7)	1,308 (74.0)

Values are n (%) unless otherwise indicated. ^aEarly presenter is defined as any participants who had their initial blood samples ≤3 hours after symptom onset.

BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; ECG = electrocardiogram; IHD = ischemic heart disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; TIA/CVA = transient ischemic attack/cerebrovascular accident.

In addition, a comparison of the safety of each ADP recommendation to rule-out (algorithm-level performance) against the actual decision of the clinician to discharge using each ADP (clinical performance) was undertaken.

ALGORITHM-LEVEL VS CLINICAL PERFORMANCE.

Algorithm-level performance refers to the recommendations of the ADP according to baseline and serial hs-cTnT values. This can include rule-out, observe, or rule-in and is independent of the clinician's decision to discharge or admit.

Clinical performance refers to the actual decision of the clinician to either discharge or admit the patient, using the randomized ADP. It may run contrary to recommendations of the ADP (in which case it is termed "a breach").

EVENT ADJUDICATION. Adjudication of all clinical endpoints in MACROS-2 (Mersey Acute Coronary Syndrome Rule-Out Study 2) was centrally coordinated. Details of the adjudication process including for representations and deaths are outlined in

Supplemental Figures 4 and 5 and the protocol.¹⁶

Agreement between the first and second adjudicator for type 1 MI was substantial (kappa = 0.77). Cardiovascular death was defined as those attributed to MI, sudden cardiac death, heart failure, stroke, cardiovascular procedures, cardiovascular hemorrhage (except major trauma), other cardiovascular causes, or those that did not have a clear non-cardiovascular cause.¹⁶

A separate hs-cTnI (Abbott Alinity) assay was used in the blinded adjudication of index MI. This was preferred over using the same hs-cTnT assay used for clinician decision making to reduce incorporation bias, a form of bias common in trials of diagnostic tests. This methodology has been used previously to compare the performance of ADPs using hs-cTns.⁷ Incorporation bias occurs when the test being assessed (hs-cTnT) is also used to define the clinical endpoint (MI). This can artificially elevate performance of the test being examined (ADPs using hs-cTnT), and although this does not completely eliminate this bias, it does mitigate it.

STATISTICAL ANALYSIS. The trial was powered on safety of discharge, defined by MACE within 30 days of discharge. To establish whether there is clinical equipoise between the ADP 0/1-hour and ADP 0/3-hour, a noninferiority analysis was performed (for assumptions and details, see protocol).

The assumed sensitivity of rule-out using the ESC 0/1-hour and 0/3-hour pathways are 99.3% and 99.8%, respectively.⁹ With a noninferiority margin of 3%, a rate for MACE at 30 days among those discharged of 10%, the estimated sample size based on 80% power with an α of 5%, and a noninferiority margin of 3% was 3,368. Allowing for a 5% loss to follow-up, the final sample size was calculated to be 3,536. The rate of discharge within 4 hours using the ESC 0/1-hour and the 0/3-hour pathways was expected to be 60% and 50%, respectively.

A sensitivity analysis was performed to assess the safety of both pathways for MACE within 30 days and subsequently index type 1 MI alone. The chi-square test was used to compare the sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) between arms. CIs for absolute differences in sensitivity, for MACE at 30 days, were calculated as 1-sided 97.5% CI using the Wilson procedure.^{18,19} Noninferiority was accepted if the lower bound of the 1-sided 97.5% CI of the sensitivity difference between pathways, for MACE within 30 days in those discharged did not exceed the 3% margin.¹⁸ Proportions of patients discharged home from the emergency department within 4 hours—or at all—

were compared using a chi-square test. Comparison of emergency department LOS was performed via a survival analysis using Kaplan-Meier curves, with patients' hospital admissions or deaths censored. All statistical tests were performed in R studio version 2024.04.1+748.

RESULTS

A total of 3,543 patients were recruited and randomized in MACROS-2: 1,769 and 1,774 in the ESC 0/1-hour and 0/3-hour cohorts, respectively. The median age was 60 years, and 53% were men (Table 1). The groups were well balanced by randomization. Approximately one-quarter (27.1%) of the population was early presenters (chest pain onset or peak to initial sample ≤ 3 hours). Demographics of the discharge populations for both ADPs are shown in Supplemental Table 2. There were no significant differences for any patient demographic across trial arms in those discharged.

A total of 13.7% (n = 486) of patients had an elevated gender specific hs-cTnI concentration, of whom 48.6% (n = 236), 9.5% (n = 46), 11.9% (n = 58), and 30.0% (n = 146) were adjudicated as experiencing type-1 MI, type-2 MI, acute myocyte injury, and chronic myocyte injury, respectively.

PRIMARY OUTCOMES. The prevalence of outcomes in all patients and specifically MACE components in those discharged from the emergency department are shown in Table 2. The adjudicated final diagnosis at 30 days was type 1 MI in 250 (7.1%) and MACE in 268 (7.6%) patients.

There was no significant difference in the proportion of patients discharged within 4 hours of presentation to the emergency department using the 0/1-hour and 0/3-hour pathways, 21.8% and 19.2%, respectively, $P = 0.07$ (Figures 2 and 3). The ESC 0/1-hour ADP did discharge a greater proportion of patients by 5 hours: 41.8% vs 32.4% respectively, $P < 0.001$ (Figure 2). However, beyond 5 hours, there remained no difference in the proportion discharged between ADPs.

The ESC 0/1-hour pathway was noninferior to the 0/3-hour pathway for MACE at 30 days in those discharged: 9 MACE events with sensitivity of 93.7% (95% CI: 88.4%-97.1%) and 13 MACE events with sensitivity of 89.5% (95% CI: 82.7%-94.3%), respectively (Figure 3). The NPV was 99.2% (95% CI: 98.6%-99.7%) and 98.9% (95% CI: 98.2%-99.4%) for the ESC 0/1-hour ADP and the 3-hour ADP, respectively. The difference in sensitivity in favor of the ESC 1-hour pathway was 4.2%, with the lower bound of the 97.5% CI: $> -3\%$ (-2.5%) (Supplemental

TABLE 2 Prevalence of Outcomes in All Patients and Those Discharged From Emergency Departments

Prevalence of Outcomes in All Patients			
	0/1 hour (N = 1,769)	0/3 hour (N = 1,774)	P Value
Events from Index Presentation			
Index Type 1 MI	123 (7.0)	113 (6.4)	N/A
Index Type 2 MI	16 (0.9)	30 (1.7)	N/A
Events Outside Index Presentation			
30/7 Type 1 MI	9 (0.5)	5 (0.3)	0.42
30/7 Urgent revascularization ^a	5 (0.3)	4 (0.2)	0.75
30/7 Cardiovascular death	6 (0.3)	3 (0.2)	0.34
30/7 All-cause death	10 (0.6)	8 (0.5)	0.81
MACE (Index and Representation Type 1 MI, Urgent Revascularization, or Cardiovascular Death)			
30/7 MACE excluding index MI	20 (1.1)	12 (0.7)	0.21
30/7 MACE	143 (8.1)	125 (7.0)	N/A
Prevalence of MACE Components in Discharged Patients			
	0/1 hour (n = 1,187)	0/3 hour (n = 1,236)	
Index type 1 MI	4 (0.3)	12 (1)	0.09
30/7 Representation type 1 MI	4 (0.3)	1 (0.1)	
30/7 Urgent revascularization	3 ^a (0.3)	1 ^a (0.1)	
30/7 Cardiovascular death	1 (0.1)	1 ^b (0.1)	1
30/7 MACE	9 (0.8)	13 (1.1)	0.58

Values are n (%). ^aAll 30/7 urgent revascularization events occurred as part of an index type 1 MI event. ^bThis cardiovascular death occurred as part of an index type 1 MI event.

MACE = major adverse cardiovascular events; other abbreviations as in Table 1.

Figure 6). All individual MACE events in the discharged population, for both pathways, are detailed in Supplemental Table 3.

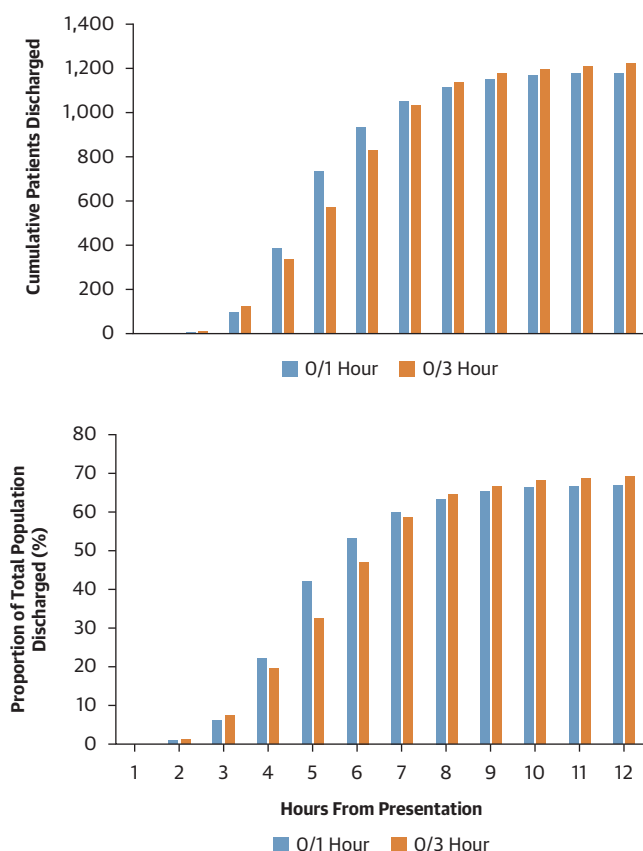
MACE events, with index MI removed, in the entire population using the ESC 1-hour ADP was not significantly different from that in the 3-hour ADP, 1.1% vs 0.7%, respectively, $P = 0.21$ (Table 2).

SECONDARY OUTCOMES. The proportion of patients discharged overall using the ESC 0/1-hour and 0/3-hour ADPs were 67.1% and 69.7%, respectively, $P = 0.11$. The median (IQR) LOS was 273 minutes (213-333 minutes) and 312 minutes (257-406 minutes) for the ESC 0/1-hour and the 0/3-hour ADPs, respectively, $P < 0.001$ (Figure 4).

The median (IQR) time from presentation to venous sampling and from venous sampling to hs-cTnT result was 47 minutes (IQR: 32-67 minutes) and 81 minutes (IQR: 69-101 minutes), respectively (Supplemental Table 4). The median repeat sampling intervals were 65 minutes (62-71 minutes) and 181 minutes (175-188 minutes) for the ESC 0/1-hour and the 0/3-hour pathways, respectively. All key sample-processing intervals were similar between trial arms (Supplemental Table 4).

The proportion of patients suitable for single sample rule-out was similar between pathways.

FIGURE 2 Cumulative and Proportion of Patients Discharged From Total Population



However, the proportion of suitable patients discharged after 1 sample was only 23% in the ESC O/1-hour arm but was 70% using the O/3-hour pathway (Supplemental Table 5).

Numerically fewer type 1 MIs were missed in those discharged using the ESC O/1-hour vs the O/3-hour ADP, although this difference was not statistically significant: 4 vs 12, respectively, $P = 0.09$. However, sensitivity and NPV point estimates for index type 1 MI did suggest superiority of the ESC O/1-hour vs the O/3-hour ADP (Supplemental Figure 7).

There was no signal of greater hazard using either pathway in those presenting within 3 hours of onset of symptoms (Supplemental Table 6).

Deviations from ADP recommendations by the managing clinician occurred in approximately one-quarter of patients managed using the ESC O/1- and the O/3-hour ADP: 25.0% vs 22.3%, respectively (Table 3).

There were 233 (20.5%) patients in the ESC O/1-hour ADP who were triaged by hs-cTnT values to observation or rule-in, but a decision was made to discharge; therefore, a pathway breach (Table 3). Of these

patients, 8 had MACE (3.4%). In the O/3-hour ADP; only 70 (6.6%) patients were discharged against pathway recommendations; and 4 experienced MACE (5.7%).

In the ESC O/1-hour arm, 194 patients (34.2%) were admitted despite fulfilling ADP rule-out criteria, of which 1 patient had a MACE (0.1%), whereas, in the O/3-hour ADP, this situation occurred in 278 patients (55.9%), and 13 had MACE (4.7%).

The algorithm-level performance (Supplemental Figures 9 and 10) of the ESC O/1-hour ADP, compared with clinician discharge, had significantly higher sensitivity and NPV for MACE at 30 days but not for index type 1 MI alone (Supplemental Table 7).

DISCUSSION

This is the first randomized trial directly comparing implementation of the ESC O/1-hour ADP with a O/3-hour ADP, both using hs-cTn assays, for suspected ACS. We report 5 major novel findings.

First, in an implementation trial of more than 3,500 patients, use of the ESC O/1-hour pathway did not alter the proportion of patients discharged from the emergency department within 4 hours of presentation. Second, there was a 39-minute reduction in median emergency department LOS using the ESC O/1-hour ADP in those discharged from the emergency department. Third, the ESC O/1-hour ADP met noninferiority for safety of clinician decision to discharge for MACE at 30 days compared with the O/3-hour ADP. Fourth, one-quarter of patients were managed against ADP recommendations. Finally, clinical performance was inferior to algorithm-level performance for MACE at 30 days using the ESC 1-hour ADP.

There have been 2 previous RCTs that have compared the safety and efficiency of the ESC O/1-hour ADP against an alternative ADP. Differences between MACROS-2 and the 2 previous RCTs^{13,14} in this space—and, in particular, the novelty of MACROS-2—is summarized in Box 1.

The ESC 1-hour ADP failed to discharge more patients than the 3-hour ADP within 4 hours, but its use did result in a median 39-minute reduction in emergency department LOS. This reduction may appear modest; however, this may be significant on a systems level, and further work, including evaluation of health care economics, is warranted.

The 39-minute reduction in LOS in MACROS-2, sits between the 2 previous RCTs in the literature.^{13,14} Median emergency department LOS was 60 minutes shorter with the ESC O/1-hour ADP in the study by Chew et al,¹³ whereas, in a stepped-wedge RCT in an

FIGURE 3 The Clinical Performance of the ESC 1-Hour Pathway and the 3-Hour Pathway for Patients Either Discharged or Admitted for MACE at 30 Days

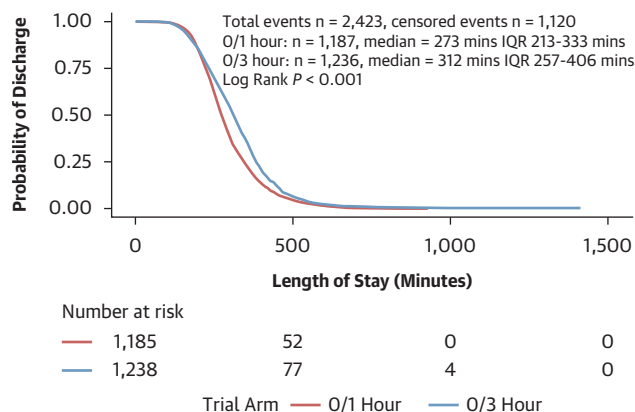
3,543 Consecutive Patients Randomized					
0/1 Hour 1,769 Patients			0/3 Hour 1,774 Patients		
		385/1,769 (21.8%)	Discharged <4 hours P Value = 0.07	341/1,774 (19.2%)	
		1,187/1,769 (67.1%)	Total Discharged P Value = 0.11	1,236/1,774 (69.7%)	
		273 minutes	Median Length of Stay P Value < 0.001	312 minutes	
Clinical Performance for MACE within 30 days in those discharged					
		MACE rate n = 9 (0.8%) Sensitivity 93.7% (88.4-97.1%) NPV 99.2% (98.6-99.7%)	P Value = 0.58 P Value = 0.21 P Value = 0.45	MACE rate n = 13 (1.1%) Sensitivity 89.5% (82.7-94.3%) NPV 98.9% (98.2-99.4%)	
		582/1,769 (32.9%)	Admitted P Value = 0.10	538/1,774 (30.3%)	
Clinical Performance for MACE within 30 days in those admitted					
		MACE rate n = 134 (23.0%) Specificity 72.4% (70.2-74.6%) PPV 23.0% (19.7-26.7%)	P Value = 0.37 P Value = 0.32 P Value = 0.34	MACE rate n = 111 (20.6%) Specificity 74.1% (71.9-76.2%) PPV 20.6% (17.3-24.3%)	

ESC = European Society of Cardiology; MACE = major adverse cardiovascular events.

Asian population by Inoue et al, there was no reduction in emergency department LOS by transferring from usual care to the ESC 1-hour ADP.¹⁴ However, the standard-care arm in this trial varied from single to serial sampling (typically more than 3 hours).

Historically, a reduction of the serial sampling interval has resulted in a reduction in emergency department LOS.^{20,21} This involved reducing the sampling interval from 12 to 6 and then 6 to 3 hours. Previously, the cTn result was often the rate-limiting step to discharge. However, when reducing the interval from 0/3 to 0/1 hour, this is often no longer the case. A reduction in this sampling interval appears to no longer translate into a significant reduction in emergency department LOS. Shortening sampling intervals (to 0/1-hour) is counter-balanced by external factors preventing early discharge (Figure 5). This assessment is further evidenced by the only modest improvements in LOS achieved by

FIGURE 4 Kaplan-Meier Curve Showing the Difference in LOS in the Emergency Department for Patients Discharged Using Either Pathway



LOS = length of stay.

TABLE 3 Pathway Breaches and Clinical Outcomes

	n (%)	Index MI	Representation Type 1 MI	Urgent Revascularization	CV Death	MACE
O/1-Hour Pathway						
Total discharged	1,139	4	4	0	1	9 (0.8)
Rule-out	906 (79.5)	1	0	0	0	1 (0.1)
Not rule-out	233 (20.5)	3	4	0	1	8 (3.4)
Total admitted	567	117	5	9	5	132 (23.3)
Rule-out	194 (34.2)	0	0	1	0	1 (0.1)
Not rule-out	373 (65.8)	117	5 ^a	8	5 ^a	131 (35.1)
Against recommendations ^b	427 (25.0)					
O/3-Hour Pathway						
Total discharged	1,065	12	1	0	1	13 (1.2)
Rule-out	995 (93.4)	8	1	0	0	9 (0.9)
Not rule-out	70 (6.6)	4	0	0	1 ^a	4 (5.7)
Total admitted	497	100	4	8	2	110 (22.1)
Rule-out	278 (55.9)	8	3 ^a	3	0	13 (4.7)
Not rule-out	219 (44.1)	92	1	5	2 ^a	97 (44.3)
Against recommendations ^b	348 (22.3)					

Values are n (%). "Rule-out" and "not rule-out" refers to accelerated diagnostic pathway recommendations. "Not rule-out" includes both observe and rule-in. ^aSome/all of these events occurred alongside an index MI event so can only trigger one MACE event. ^bTotal patients whose clinician managed them against pathway recommendations, either to discharge to admit.
CV = cardiovascular; other abbreviations as in [Tables 1 and 2](#).

introduction of hs-cTn point-of-care assays, which significantly reduce sample turnaround time.²²⁻²⁴

The Kaplan-Meier curves for length of stay between MACROS-2 and RAPID-TnT (Rapid Assessment of Possible ACS in the Emergency Department With High-Sensitivity Troponin T Trial), by Chew et al¹³ are similar and both diverge after 3 hours. This is caused by single sample rule-out, which is common to both pathways and allows discharge after only 1 hs-cTnT sample.

Central laboratory sample turnaround times, 81 minutes ([Supplemental Table 4](#)) in this trial, are likely to be a significant factor explaining the modest reduction in emergency department LOS for the ESC O/1-hour ADP. The proportion of patients whose initial result was not available to review at the time of repeat sample collection, using the ESC O/1-hour and O/3-hour ADP, were 78.5% and 5.6%, respectively. Therefore, 23% and 70.1% of those suitable for single sample rule-out were discharged without a repeat sample using the ESC O/1-hour and the O/3-hour ADP, respectively ([Supplemental Table 5](#)). This partly explains the narrowing of the discharge times.

In addition, all sampling intervals were equal across trial arms ([Supplemental Table 4](#)). Therefore, we can be confident that any differences in LOS can be attributed to the reduction in the sampling intervals between pathways.

No previous study has been able to directly compare either (O/1 or O/3) ADPs safety of clinician decision to discharge, with the universal use of high-

sensitive troponins, and with formal adjudication with an independent hs-cTn to reduce incorporation bias. Previous RCTs have compared safety between ADPs across the entire intention to treat population using representation events only, thus excluding index MI.^{13,14} In contrast, we chose to compare safety of clinician decision to discharge using the randomized ADP, which enabled inclusion of the index MI event. Once patients are admitted, the impact of the randomized ADP used in the emergency department has on their subsequent care is unlikely to be significant.

Multiple previous observational studies and 1 meta-analysis have assessed the algorithm-level performance of the ESC O/1-hour ADP, using hs-cTnT.^{3,7,9-11,15,25-28} The pooled sensitivity of the

BOX 1 How MACROS-2 Extends Previous Randomized Trials of Accelerated Diagnostic Pathways

- First patient-level randomized controlled trial to compare safety and efficiency of the ESC O/1-hour ADP against a O/3-hour ADP, with both ADPs universally using a high-sensitive cardiac troponin.
- Blinded adjudication of index MI endpoint using an independent hs-cTnI assay, to minimize incorporation bias.
- Comparison of safety of clinician decision to discharge (as part of 30 day MACE), using a detailed blinded adjudication process for MI.
- Comparison of algorithm-level vs clinical performance for the 2 ADPs.
- Details of pathway breaches and direct impact on ADP performance.

ADP = accelerated diagnostic pathway; ESC = European Society of Cardiologists; MACE = major adverse cardiovascular events; MI = myocardial infarction.

ESC 0/1-hour and 0/3-hour ADP, using hs-cTnT, in a meta-analysis was 99.2% (95% CI: 98.5%-99.6%) and 95.0% (95% CI: 84.9%-98.5%), respectively.³ These studies used adjudicated index MI alone as the primary endpoint. Although the findings in this trial are directionally consistent, the sensitivity for index MI alone, in those discharged, was lower for both the ESC 0/1-hour and 0/3-hour ADPs. This emphasizes the potential difference between extrapolation based on algorithm-level performance, which is common in observational studies and implementation and clinical performance based on actual decision making.

The cohort of patients termed "early presenters" is notoriously challenging for ADPs. Importantly, in this subgroup analysis there was no signal that either pathway performed worse in this cohort (Supplemental Table 6).

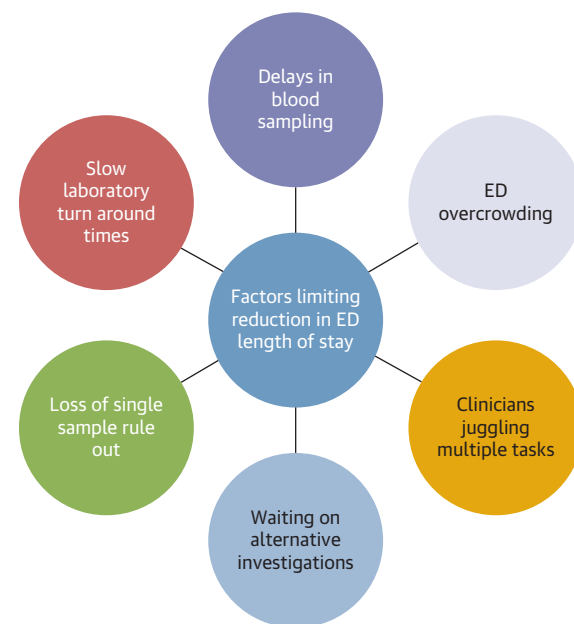
Extrapolation of times and results in observational studies to likely gains in early discharge is often a driver for change and even guideline updating. However, actual clinical performance in those discharged was significantly lower than algorithm-level recommended rule-out for MACE at 30 days, sensitivity 93.7% (88.4%-97.1%) vs 98.6% (95.0%-99.8%) (Supplemental Table 7). This finding indicates that real-world clinical performance may be inferior to what is suggested in observational studies. Further trials are needed to validate this important finding.

Our trial suggests that up to one-quarter of patients are managed against the recommendation of the ADP by their clinician. Patients may be discharged when triaged to observe or rule-in for many reasons including the following: overcrowded emergency departments, a perceived stringency to rule-out in the ADP or difficulty in interpreting the pathway. Conversely, admission of patients triaged to rule-out may be as a result of an ischemic electrocardiogram (ECG), concerning symptomatology, other medical issues requiring admission, or pressure on clinicians to move patients from the emergency department.

When implemented into clinical practice, an ADP's clinical performance and discharge potential may differ from what is reported in observational studies, which cannot account for these factors. The majority of MACE in discharged patients in the ESC 0/1-hour arm came from patients managed against ADP recommendations. Interestingly, this was not the case for the 0/3-hour ADP. Importantly, although our data can highlight these possible differences, our trial is underpowered to confirm these with certainty.

A key strength of MACROS-2 is its meticulous adjudication of endpoints. Clinical decision making

FIGURE 5 Factors That Limit Improvements in Emergency Department LOS With Shortening Sampling Intervals



Abbreviation as in Figure 4.

was undertaken using a hs-cTnT assay, but adjudication of type 1 MI was undertaken using an independent hs-cTnI assay, with adjudicators blind to the hs-cTnT results. This methodology reduces incorporation bias, which is typical in trials of diagnostic tests but has rarely been adopted in clinical research.²⁹

STUDY LIMITATIONS. There are some limitations to MACROS-2 that should be considered. First, it was trial staff that took all hs-cTn sampling for patients recruited. MACROS-2 is therefore a comparison of both pathways impact on departmental efficiency in a best-case scenario for both pathways.

Second, because of staffing for the trial, recruitment only took place during the day. We therefore cannot comment on the impact of these pathways on the efficiency of the emergency department overnight.

This trial is from 2 large emergency departments in Northern England, with mostly a Caucasian population, and therefore the validity of these findings to other populations, such as those in North America, or those with higher mixed or predominantly Black or Asian populations, can be questioned. However, the incidence of type 1 MI aligns with other studies in a Western population.

We chose to measure our primary safety endpoint in the discharged population, not our entire randomized population. The sample size calculations were based on the presumed numbers of patients eligible for discharge from either pathway based on historical precedent. Thus, our primary analysis does not encompass the entire randomized population but a subset. This could introduce a bias. However, patient demographics across trial arms in those discharged generally were not different than the entire trial population (Supplemental Table 2). In the context of specific treatments, such as pharmacotherapy, it is therefore not an "intention-to-treat population." However, a selective focus on discharges is important, given that an ADP's primary role is to safely triage low-risk patients to discharge. This decision to include index MI greatly improved our statistical power to detect a difference in safety for those discharged between the ADPs. When the entire randomized cohort was included, without the inclusion of index MI, there was no difference in rate of MACE between ADPs. It is important to state that there was insufficient power to determine any differences when using the entire population with index MI excluded, and therefore there is the possibility of a type 2 error. A sample size of >25,000 would be required to discern differences in representation MI and cardiac death between pathways, given the very low rate of events.

Our study was underpowered for early discharge as the proportions discharged early was much lower than predicted. Our sample size was predicated on an event rate, in those discharged, of 10% for MACE at 30 days.¹⁶ The actual MACE rate in MACROS-2 was 7.6%. However, given the direction of findings it is highly unlikely that the noninferiority of the ESC 0/1-hour compared with the 0/3-hour ADP could be overturned by a slightly higher event rate.

CONCLUSIONS

In this implementation RCT of greater than 3,500 patients, the ESC 0/1-hour ADP failed to discharge more patients within 4 hours than the 0/3-hour pathway. Its use resulted in a modest median 39-minute reduction in LOS. Clinical performance of the ESC 0/1-hour ADP in those discharged was non-inferior to the 0/3-hour pathway.

This trial highlights the challenges of implementing ADPs into clinical practice and that real-world clinical performance may be inferior to that implied by observational, algorithm-level studies. In addition, an ever-decreasing sampling interval may result in a rule of diminishing returns (in terms of early discharge). This is likely because of a combination of

factors such as emergency department overcrowding, system inefficiencies and constraints, and central laboratory turnaround times.

DATA AVAILABILITY The entire dataset for MACROS 2 is in REDCAP Vanderbilt, licensed to the University of Liverpool. Application for the entire deidentified dataset should be made through e-mailing the corresponding author.

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APPENDIX For supplemental tables and supplemental figures, please see the online version of this paper.