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Early computed tomography coronary angiography and preventative treatment in patients with suspected acute coronary syndrome: A secondary analysis of the RAPID-CTCA trial

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Background Computed tomography coronary angiography (CTCA) offers detailed assessment of the presence of coronary atherosclerosis and helps guide patient management. We investigated influences of early CTCA on the subsequent use of preventative treatment in patients with suspected acute coronary syndrome.

Methods In this secondary analysis of a multicenter randomized controlled trial of early CTCA in intermediate-risk patients with suspected acute coronary syndrome, prescription of aspirin, P2Y₁₂ receptor antagonist, statin, renin-angiotensin system blocker, and beta-blocker therapies from randomization to discharge were compared within then between those randomized to early CTCA or to standard of care only. Effects of CTCA findings on adjustment of these therapies were further examined.

Results In 1,743 patients (874 randomized to early CTCA and 869 to standard of care only), prescription of P2Y₁₂ receptor antagonist, dual antiplatelet, and statin therapies increased more in the early CTCA group (between-group difference: 4.6% [95% confidence interval, 0.3-8.9], 4.5% [95% confidence interval, 0.2-8.7], and 4.3% [95% confidence interval, 0.2-8.5], respectively), whereas prescription of other preventative therapies increased by similar extent in both study groups. Among patients randomized to early CTCA, there were additional increments of preventative treatment in those with obstructive coronary artery disease and higher rates of reductions in antiplatelet and beta-blocker therapies in those with normal coronary arteries.

Conclusions Prescription patterns of preventative treatment varied during index hospitalization in patients with suspected acute coronary syndrome. Early CTCA facilitated targeted individualization of these therapies based on the extent of coronary artery disease. (Am Heart J 2023;266:138–148.)

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Background

Preventative treatment is the cornerstone of ongoing management for patients with acute coronary syndrome as many of these patients remain at high risk for recurrent atherothrombotic events throughout their lifetime.¹⁻⁴ Pharmacological prevention, such as antithrombotic, lipid-lowering, and neurohormonal modulation therapies, reduces downstream ischemic events and improves survival after index acute coronary syndrome. Current practice guidelines recommend antiplatelet and statin therapies as routine preventative treatment for all patients and renin-angiotensin system blocker and beta-blocker therapies in selected patients at higher risk.⁵

Patients with suspected acute coronary syndrome are a heterogeneous group and undergo diagnostic evaluation and risk stratification, using electrocardiography, cardiac troponin testing, and clinical risk scoring, eg, the Global Registry of Acute Coronary Events (GRACE) score, to assist clinical decision making.⁶ However, these measures can neither confirm nor refute the presence of coronary atherosclerosis, which, when identified, would modify management by facilitating the use of tailored guideline-directed preventative treatment, which, by contrast, would not be employed in those if they were found to have normal coronary arteries. Computed tomography coronary angiography (CTCA) can noninvasively identify the extent of coronary artery disease with comparable effectiveness to invasive coronary angiography.⁷ Moreover, CTCA detects anatomically less severe but prognostically more important coronary atherosclerosis.^{8,9} In the Scottish Computed Tomography of the Heart (SCOT-HEART) trial, CTCA improved the long-term clinical outcome that, in part, appeared to be attributable to better targeting of preventative treatment in patients with stable chest pain.^{10,11} However, whether CTCA has similar utility in guiding the use of these therapies in patients with acute chest pain due to suspected acute coronary syndrome is currently unknown.

The Rapid Assessment of Potential Ischaemic Heart Disease with CTCA (RAPID-CTCA) trial of early CTCA in intermediate-risk patients with suspected acute coronary syndrome has reported that the overall frequency of prescription of preventative treatment was similar between those managed with early CTCA or with standard of care only.¹² Nevertheless, this did not take into account individual therapies, their adjustment, nor the direct influence of CTCA findings on those treatment decisions. In this secondary analysis, we aimed to investigate impacts of early CTCA on the nature of prescription of preventative treatment and to examine the differential effects of the presence or absence of coronary atherosclerosis by CTCA on treatment adjustment.

Methods

Trial overview

The design of the RAPID-CTCA trial (ClinicalTrials.gov identifier, NCT02284191) has been reported previously.¹³ In brief, this multicenter prospective randomized open-label blinded endpoint trial enrolled intermediate-risk patients with suspected acute coronary syndrome and a history of coronary artery disease, an abnormal electrocardiogram, or an elevated cardiac troponin concentration from March 2015 to June 2019. Patients with any symptoms, signs, or investigations supporting high-risk acute coronary syndrome were not eligible. Moreover, those who could not undergo CTCA and those who had either evident obstructive coronary artery disease (within 2 years) or normal coronary arteries (within 5 years) were excluded.

Patients were randomly assigned 1:1, stratified by site, in permuted blocks of varying sizes (4-8), to receive either early CTCA in addition to standard of care or standard of care only. All clinical teams were provided with guidance on management based on CTCA findings (Supplementary Table 1). And CTCA results, when available, were communicated immediately to treating physicians.

The South East Scotland Research Ethics Committee approved the trial. All patients gave written informed consent.

Preventative treatment

Prescribing data before and during index hospitalization were recorded in the trial database as therapeutic classes, including timing of initiation and cessation of these therapies. When the same medication remained throughout hospitalization, any dose alterations were recorded by the research team. The 5 drug classes of interest in this study were aspirin, P2Y₁₂ receptor antagonist, statin, renin-angiotensin system blocker, and beta-blocker therapies.

To assess effects of trial intervention on prescription and adjustment of preventative treatment, we only analyzed prescribing data from randomization to discharge. Prescription at randomization was defined as medications prescribed before and continued up to or prescribed at the time of randomization. Prescription at discharge was defined as medications continued beyond or prescribed at the time of discharge.

Statistical analysis

Descriptive data were summarized with median (interquartile range) for continuous variables and frequency (percentage) for categorical variables, and differences were compared with the Mann-Whitney *U* test and the Fisher-Freeman-Halton test as appropriate.

The primary analysis was performed using the intention-to-treat principle. Group-specific effects on

prescription of preventative treatment were estimated by the generalized estimating equation for Poisson regression analysis, with an unstructured covariance matrix, to account for the clustering effect (individual patients), and intervention effects (between-group differences) on prescription of preventative treatment were examined with the use of a 2- (study group-by-time) or 3-way (subgroup level-by-study group-by-time) interaction as appropriate. In addition, adjustment of these therapies by study group then by CTCA finding in the early CTCA group was first evaluated using the Fisher-Freeman-Halton test then by *post hoc* ordinal or Firth logistic regression analysis where appropriate.

Two *post hoc* sensitivity analyses were conducted. To account for effects of coronary artery anatomy visualized by invasive coronary angiography, data were limited to patients who underwent invasive coronary angiography at index hospitalization and were further stratified by whether subsequent coronary revascularization was performed during the same hospitalization in the first sensitivity analysis. Since the RAPID-CTCA trial was a pragmatic study in the emergency care setting, patients were permitted to undergo ambulatory CTCA (if being assigned to the early CTCA group) or to cross over to CTCA (if being assigned to the standard of care only group). Among those randomized to early CTCA, about a tenth underwent CTCA after discharge, and another 12% did not undertake or complete the scan at all. An as-tested population based on the actual intervention received before discharge and by CTCA finding was examined in the second sensitivity analysis.

This study was exploratory with no adjustment for multiplicity undertaken, and patients who died at index hospitalization were not included. All analyses were performed using SAS software, version 9.4 (SAS institute, Cary, NC).

Results

Baseline characteristics

Of 1,748 patients reported in the primary study analysis, 5 (0.3%) were excluded due to in-hospital death (Figure 1).

The median age of patients was 61 (interquartile range: 52-71) years, and 634 (36.4%) were women. At presentation, 598 (34.3%) patients had prior coronary artery disease, 1,060 (60.8%) had an abnormal electrocardiogram, and 1,001 (57.4%) had an elevated cardiac troponin concentration. Overall, 369 (36.7%) patients were considered at high suspicion of acute coronary syndrome by their physician, and the median GRACE score was 113 (interquartile range: 91-137). At randomization, 1,040 (59.7%) patients were routinely prescribed aspirin, 701 (40.2%) received a P2Y₁₂ receptor antagonist, and altogether 611 (35.1%) had dual antiplatelet therapy. For other preventative therapies, 683 (39.2%),

564 (32.4%), and 629 (36.1%) patients were routinely prescribed statin, renin-angiotensin system blocker, and beta-blocker therapies, respectively. Patient characteristics and the use of preventative treatment were well balanced between the 2 study groups (Table 1).

At index hospitalization, the frequency of noninvasive testing for myocardial ischemia was higher in the standard of care only group, whereas there was no difference in the use of invasive coronary angiography between the 2 study groups (Supplementary Table 2).

Prescription of preventative treatment from randomization to discharge

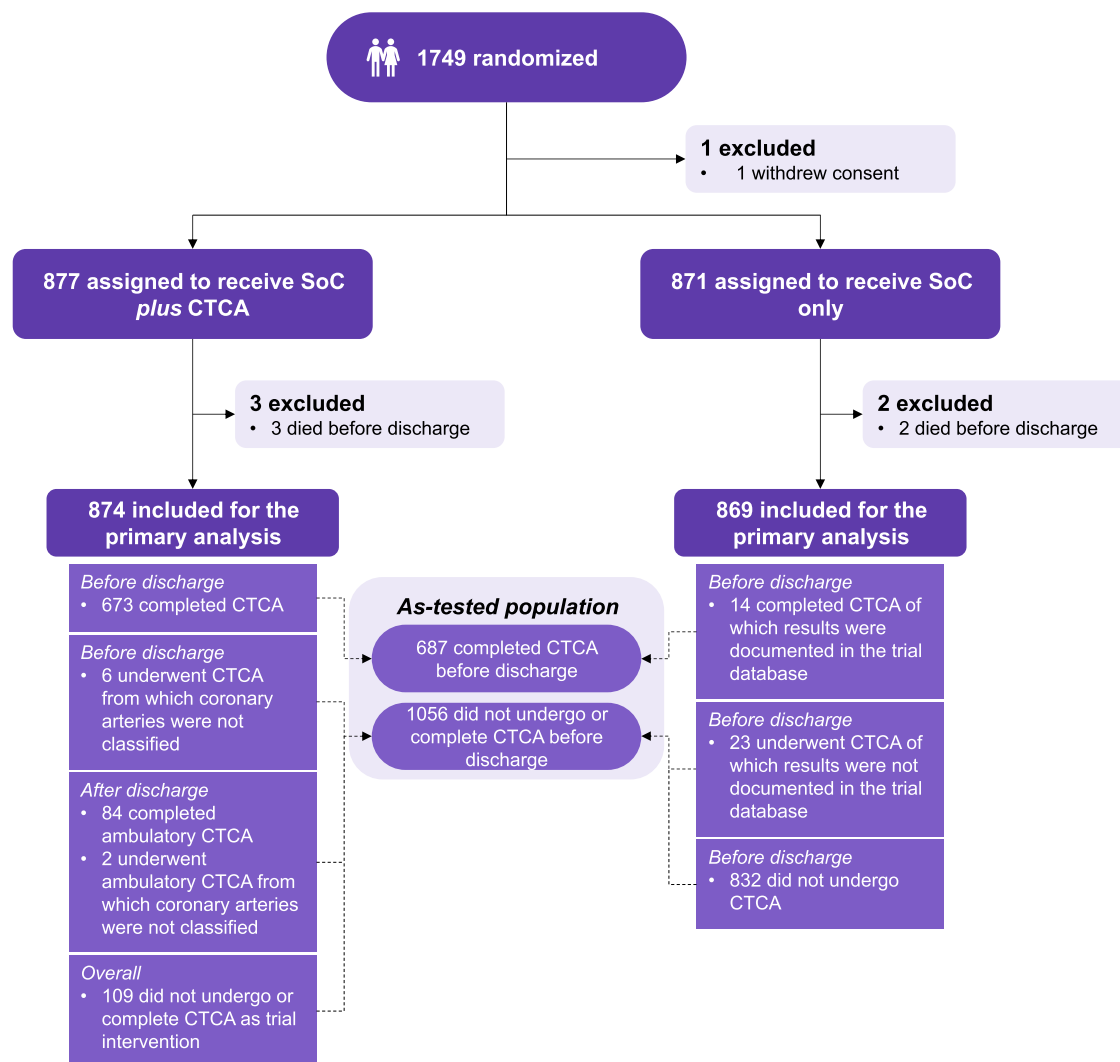
The patterns of prescription of antiplatelet therapies differed in the 2 study groups (Figure 2A). The proportions of patients prescribed aspirin, a P2Y₁₂ receptor antagonist, and dual antiplatelet therapy rose in the early CTCA group but remained unchanged in the standard of care only group. Although there was a tendency towards an additional increase in prescription of aspirin favoring early CTCA, the effect size was modest and failed to achieve statistical significance (Supplementary Table 3). Meanwhile, between-group comparisons demonstrated small increases in the proportions of patients prescribed a P2Y₁₂ receptor antagonist (4.6%; 95% confidence interval, 0.3-8.9) and dual antiplatelet therapy (4.5%; 95% confidence interval, 0.2-8.7) in the early CTCA group. In contrast, the proportions of patients prescribed other preventative therapies increased in both study groups from randomization to discharge (Figure 2B). And there was a further growth in the proportion of patients prescribed statin therapy (between-group difference: 4.3%; 95% confidence interval, 0.2-8.5) in the early CTCA group.

Regardless of prior coronary artery disease, results of the electrocardiogram and their cardiac troponin testing, projected risk levels by GRACE score, or levels of suspicion of acute coronary syndrome, intervention effects were consistent across subgroups of interest (Figure 3).

Adjustment of preventative treatment

Apart from initiation and cessation of preventative treatment, a small percentage of patients had dose or potency alterations for their therapies (Supplementary Table 4). Together, the overall proportions of patients who had their preventative treatment adjusted were broadly similar between the 2 study groups except for statin therapy (Table 2). Among those who had preventative treatment adjusted, early CTCA was associated with a greater number of patients who started a P2Y₁₂ receptor antagonist or altered from clopidogrel to prasugrel or ticagrelor (odds ratio, 1.46; 95% confidence interval, 1.01-2.11; $P = .043$) or started dual antiplatelet therapy (odds ratio, 1.54; 95% confidence interval, 1.01-2.35; $P = .043$) (Supplementary Figure 1).

Figure 1



Study flowchart. CTCA, computed tomography coronary angiography; SoC, standard of care.

Influences of CTCA findings

Among patients randomized to early CTCA, adjustment of preventative treatment varied substantially by CTCA finding (Figure 4). Compared to those 201 patients who did not undergo or complete CTCA by discharge or had an unclassified scan, there were higher rates for increments of all preventative treatment except for aspirin in those with obstructive coronary artery disease, and rates for reductions of antiplatelet and beta-blocker therapies were greater in those with normal coronary arteries.

Sensitivity analyses

Restricting analysis to patients undergoing invasive coronary angiography at index hospitalization showed

that prescription of all antiplatelet therapies (including aspirin) increased more in the early CTCA group (Supplementary Table 5). There was also a tendency towards greater increases in prescription of these antiplatelet therapies among patients who did not undergo subsequent coronary revascularization during the same hospitalization than among those who did.

The results of the as-tested population were congruous with the findings limited to patients randomized to early CTCA, supporting knowledge of coronary artery anatomy dominated treatment decisions: prescription of preventative treatment, including aspirin, increased to a greater extent in those with obstructive coronary artery disease and increased to a lesser extent (for statin, renin-angiotensin system blocker, and the beta-blocker

Table 1. Baseline characteristics

	Early CTCA (N = 874)	SoC only (N = 869)	P value
Age, years	61 (53-71)	61 (52-70)	.345
Female sex	313 (35.8)	321 (36.9)	.654
Diabetes mellitus	151 (17.3)	165 (19.0)	.384
Hypertension	410 (46.9)	402 (46.3)	.810
Dyslipidemia	356 (40.7)	335 (38.6)	.353
Prior cerebrovascular disease	34 (3.9)	38 (4.4)	.632
Prior peripheral vascular disease	27 (3.1)	28 (3.2)	.892
Prior coronary artery disease	300 (34.3)	298 (34.3)	>.999
Abnormal electrocardiogram at presentation	546 (62.5)	514 (59.1)	.169
Elevated cardiac troponin at presentation	489 (55.9)	512 (58.9)	.226
High clinical suspicion of acute coronary syndrome	317 (36.3)	322 (37.1)	.766
Systolic blood pressure, mm Hg	137 (123-154)	137 (122-152)	.830
Diastolic blood pressure, mm Hg	79 (69-88)	78 (70-88)	.858
Heart rate, beats/min	69 (61-78)	70 (62-79)	.325
GRACE score	113 (91-139)	114 (91-137)	.950
Hospital attendance to randomization, hours	10 (4-17)	10 (4-17)	.844
Preventative treatment at randomization			
Aspirin	509 (58.2)	531 (61.1)	.241
P2Y ₁₂ receptor antagonist	352 (40.3)	349 (40.2)	>.999
Dual antiplatelet therapy	307 (35.1)	304 (35.0)	.960
Statin	329 (37.6)	354 (40.7)	.202
RAS blocker	283 (32.4)	281 (32.3)	>.999
Beta-blocker	316 (36.2)	313 (36.0)	.960

Data are median (interquartile range) or n (%).

CTCA, computed tomography coronary angiography; GRACE, Global Registry of Acute Coronary Events; RAS, renin-angiotensin system; SoC, standard of care.

Table 2. Adjustment of preventative treatment

	Early CTCA (N = 874)	SoC only (N = 869)	P value
Aspirin	126 (14.4)	120 (13.8)	.731
P2Y ₁₂ receptor antagonist	211 (24.1)	204 (23.5)	.779
Dual antiplatelet therapy	183 (20.9)	176 (20.3)	.767
Statin	290 (33.2)	247 (28.4)	.033
RAS blocker	143 (16.4)	149 (17.1)	.700
Beta-blocker	189 (21.6)	182 (20.9)	.770

CTCA, computed tomography coronary angiography; RAS, renin-angiotensin system; SoC, standard of care.

Data are n (%).

Dose and potency (between clopidogrel and prasugrel or ticagrelor) alterations were included for P2Y₁₂ receptor antagonist therapy.

Only initiation and cessation were included for dual antiplatelet therapy.

Differences were compared by the Fisher-Freeman-Halton test.

therapies) or even reduced (for antiplatelet therapies) in those with normal coronary arteries compared to those who did not undertake or complete CTCA by discharge or had an unclassified scan (Supplementary Figure 2; Supplementary Table 6).

Discussion

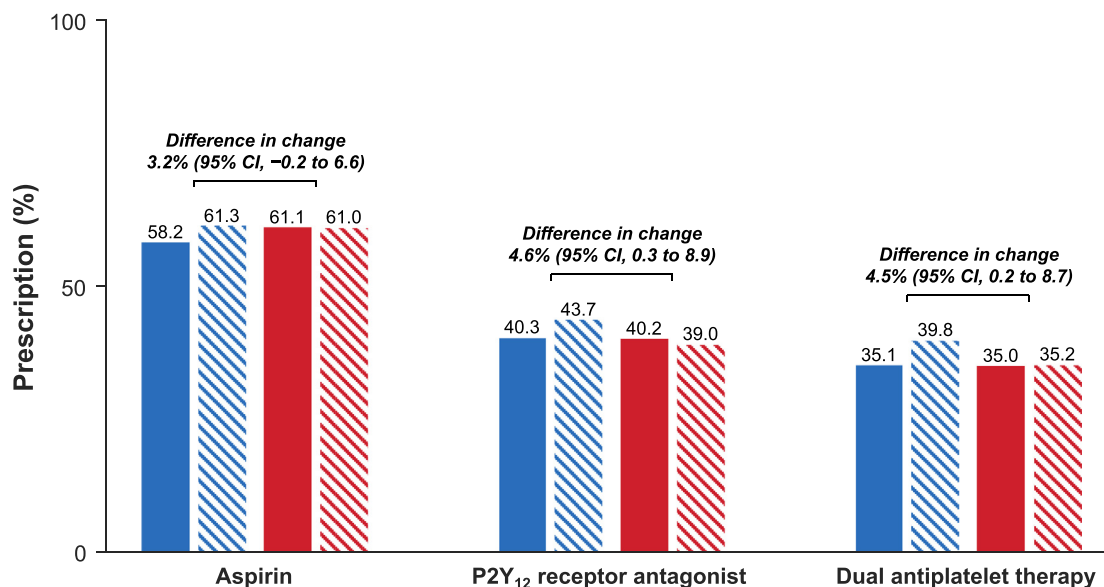
In this secondary analysis of the RAPID-CTCA trial, we found that prescription of all preventative treatment except for antiplatelet therapies increased during index hospitalization in both study groups. Early CTCA led to further growths in prescription of P2Y₁₂ receptor antagonist-based and statin therapies. Overall, early CTCA was associated with adjustment of preventative treatment dictated by the presence or absence of coro-

nary atherosclerosis: those with obstructive coronary artery disease were more likely to receive intensification of their P2Y₁₂ receptor antagonist-based, statin, renin-angiotensin system blocker, and beta-blocker therapies and those with normal coronary arteries were more likely to have a reduction in their antiplatelet and beta-blocker therapies. Thus, early CTCA has a direct influence upon the application of preventative treatment in intermediate-risk patients with suspected acute coronary syndrome.

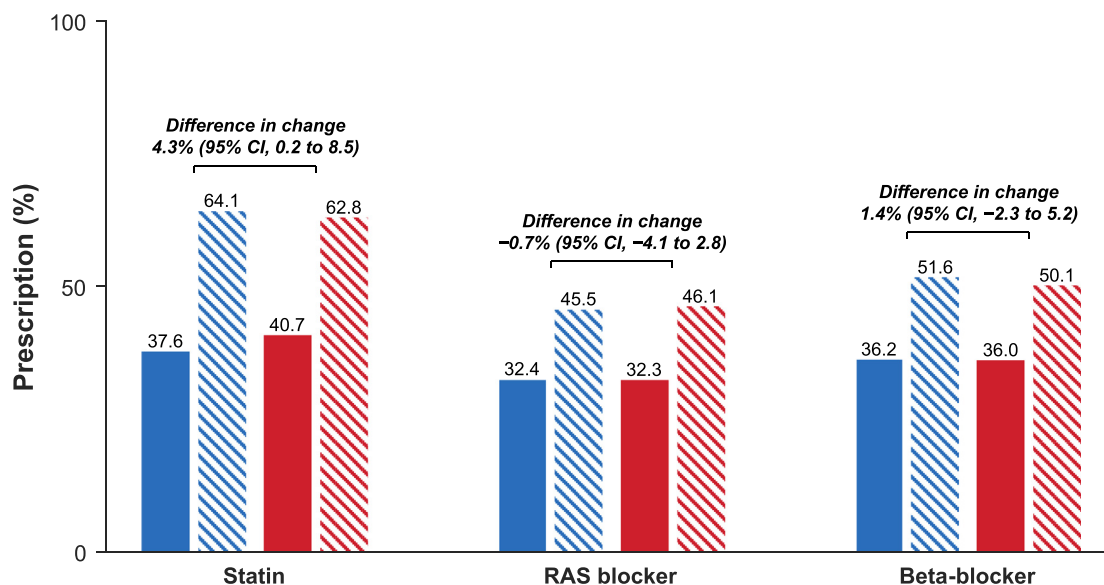
We have previously reported a similar overall frequency of prescription of preventative treatment between the 2 study groups.¹² However, this detailed exploratory analysis of these data has indicated that there were modest variations between individual therapies. Early CTCA did not demonstrably amend prescription

Figure 2

A. Antiplatelet therapy



B. Other preventative therapy

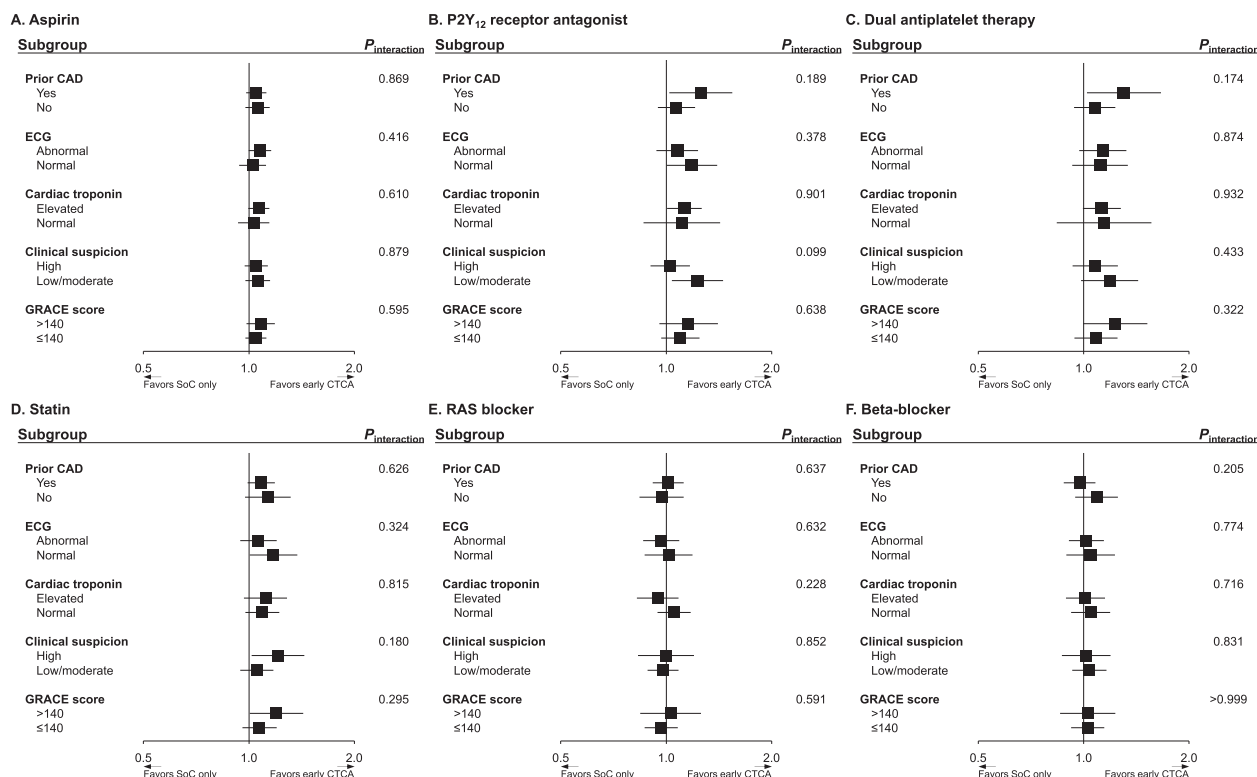


Prescription of preventative treatment. *CI*, confidence interval; *CTCA*, computed tomography coronary angiography; *RAS*, renin-angiotensin system; *SoC*, standard of care. *Blue bars represent the early CTCA group; red bars represent the SoC only group. †Solid bars represent prescription at randomization; hatched bars represent prescription at discharge.

of aspirin, renin-angiotensin system blocker, and beta-blocker therapies in these intermediate-risk patients. Earlier studies of patients with a normal electrocardiogram and cardiac troponin concentration also suggested that CTCA did not modify prescription of aspirin and statin therapies in low-risk patients.¹⁴⁻¹⁶ These pieces of evi-

dence collectively confirm that aspirin, statin, and beta-blocker therapies are part of standard clinical pathways for suspected acute coronary syndrome.¹⁷ In contrast to low-risk patients, we have shown that early CTCA was associated with increased prescription of P2Y₁₂ receptor antagonist-based and statin therapies. This difference is

Figure 3



Between-subgroup differences in prescription of preventative treatment. CAD, coronary artery disease; CTCA, computed tomography coronary angiography; ECG, electrocardiogram; GRACE, Global Registry of Acute Coronary Events; RAS, renin-angiotensin system; SoC, standard of care. *Squares are relative rate ratios comparing early CTCA with SoC only. †Horizontal lines indicate 95% confidence intervals. ‡Values of $P_{\text{interaction}}$ reflect the testing of 3-way interactions between subgroup level, study group (early CTCA vs SoC only), and time (discharge vs randomization).

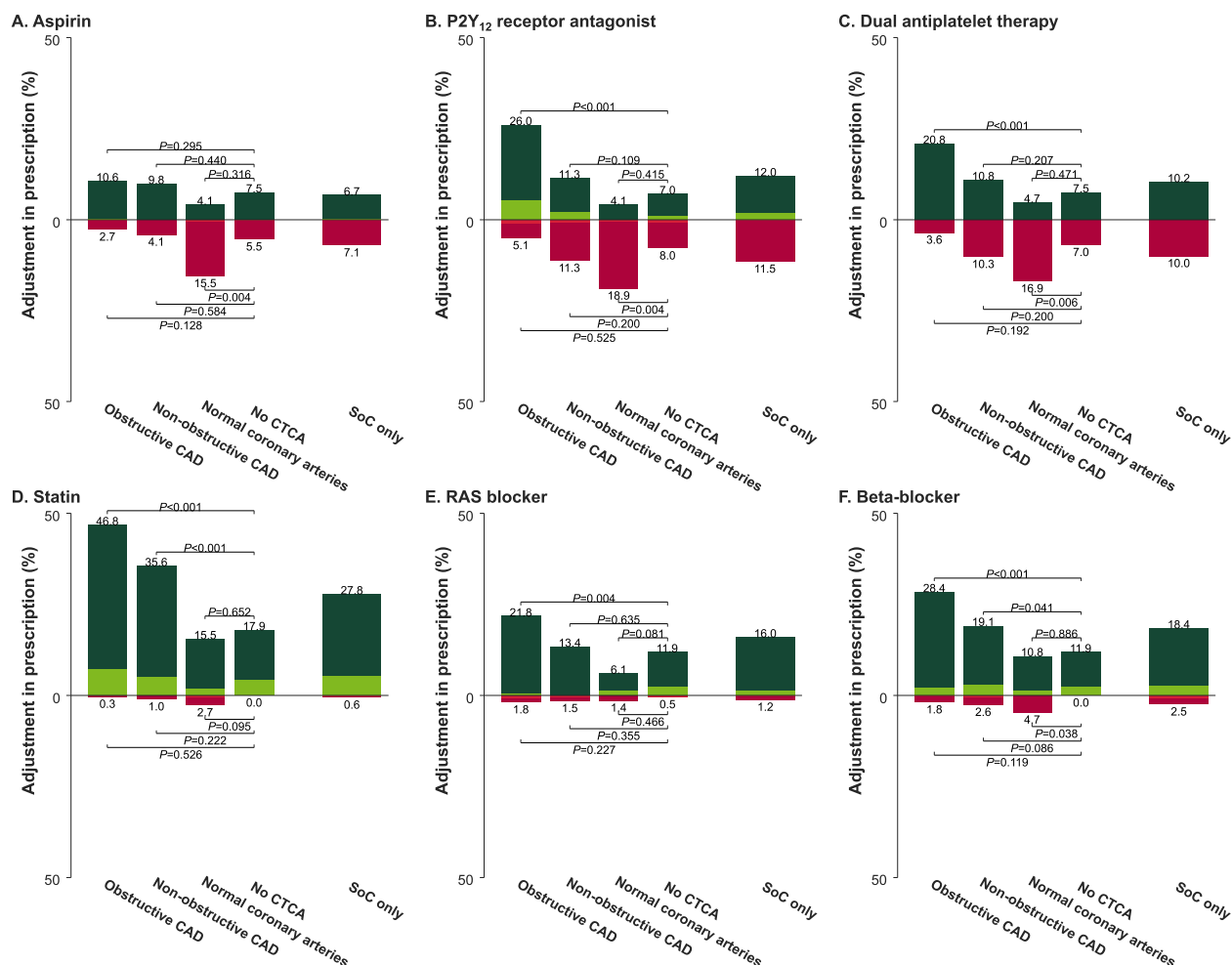
largely determined by the underlying prevalence of acute coronary syndrome, where treating physicians would reserve treatment decisions, particularly regarding prescription of a P2Y₁₂ receptor antagonist, until anatomical characterization of coronary arteries has occurred for most patients. This is consistent with our subgroup analysis which indicated that early CTCA was associated with a qualitatively greater increase in prescription of a P2Y₁₂ receptor antagonist in those at low-to-moderate suspicion of acute coronary syndrome, in whom an invasive strategy and therefore prescription of a P2Y₁₂ receptor antagonist are usually not defaults.^{18,19}

Current practice guidelines recommend early anatomical characterization of coronary arteries to determine subsequent management in patients with non-ST-segment elevation acute coronary syndrome, particularly optimization of dual antiplatelet therapy, to balance between ischemic benefit and hemorrhagic harm.²⁰⁻²² We have reported that early CTCA enhanced selection of patients with suspected acute coronary syndrome for in-

vasive coronary angiography and subsequent coronary revascularization regardless of cardiac troponin elevation.²³ In this current analysis, we have shown that early CTCA was consistently associated with an increase in prescription of a P2Y₁₂ receptor antagonist irrespective of cardiac troponin concentrations. When further refining our analysis to those who underwent invasive coronary angiography at index hospitalization, we demonstrated that early CTCA increased prescription of both aspirin and a P2Y₁₂ receptor antagonist. In addition, these differences were readily apparent in patients who did not undertake coronary revascularization, consistent with the greater detection of nonobstructive coronary artery disease with CTCA.⁷ Taken together, these results indicate that early CTCA is a useful gatekeeper in identifying appropriate candidates for coronary revascularization and dual antiplatelet therapy in patients with suspected acute coronary syndrome.

Although management of acute coronary syndrome is well established based on the presence and extent of ob-

Figure 4



Adjustment of preventative treatment by CTCA finding in the early CTCA group. CAD, coronary artery disease; CTCA, computed tomography coronary angiography; RAS, renin-angiotensin system; SoC, standard of care. *No adjustment for multiplicity was undertaken. †Dark green bars represent initiation of therapies and light green bars represent up-titration of therapies; dark red bars represent cessation of therapies and light red bars represent down-titration of therapies. ‡Because of sparse data for up-titration and down-titration of therapies, initiation and up-titration were collapsed into one categorical level and cessation and down-titration into another before being tested with Firth logistic regression analysis. §Of 874 patients randomized to early CTCA, 195 did not undergo or complete the scan by discharge and 6 had an unclassified scan. These 201 patients were included in the 'No CTCA' subgroup. Among those with obstructive CAD, 86 (including 18 altered to prasugrel or ticagrelor) intensified P2Y₁₂ receptor antagonist therapy, 69 started dual antiplatelet therapy, 155 (including 24 increased dose) intensified statin therapy, 72 (including 2 increased dose) escalated RAS blocker therapy, and 94 (including 7 increased dose) escalated beta-blocker therapy. In contrast, among those with normal coronary arteries, 23 (including 1 decreased dose) reduced aspirin therapy, 28 (including 1 altered to clopidogrel) reduced P2Y₁₂ receptor antagonist therapy, 25 stopped dual antiplatelet therapy, and 7 stopped beta-blocker therapy.

structive coronary artery disease identified by invasive coronary angiography, formulating a treatment consensus based on CTCA findings may have a prognostic implication. In the Cardiac cT in the treatment of acute CHest pain (CATCH) trial, recommendations regarding an invasive strategy were made based on the presence of CTCA-

defined obstructive coronary artery disease. The CATCH trial demonstrated that CTCA resulted in greater prescription of aspirin and a P2Y₁₂ receptor antagonist and appeared to improve the longer term clinical outcome.²⁴ In addition to recommendations on invasive coronary angiography, management guidance implemented in the

RAPID-CTCA trial may have further informed the use of preventative treatment, and our results showed that there was a gradient of adjustment of preventative treatment by CTCA finding, particularly antiplatelet therapies were reduced in patients with normal coronary arteries.

The SCOT-HEART trial underscored the long-term cardiovascular benefit of early and persistent, targeted prescription of antiplatelet and statin therapies guided by CTCA.²⁵ Compared to the SCOT-HEART trial and the CATCH trial both showing an approximately 10% increase in antiplatelet or statin therapies, the impact of early CTCA on the use of these therapies was modest in the RAPID-CTCA trial, and therefore the benefit would be expected to take longer time to accrue if these therapies had continued. Although early CTCA is unlikely to modify the immediate or intermediate outcome in every patient with suspected acute coronary syndrome, a subset of those who have myocardial infarction excluded by cardiac troponin testing but remain at high risk may offer a great opportunity for CTCA to improve their long-term outcome by targeted individualization of preventative treatment.²⁶ More importantly, had these therapies not been prescribed at index hospitalization, the probability of treatment initiation may be limited.²⁷ In fact, nearly 30% of patients with nonobstructive coronary artery disease in the RAPID-CTCA trial were not prescribed statin therapy, which highlights a potential tendency to streamline the clinical pathway in the busy emergency care setting by dichotomizing treatment strategies into only treating patients with obstructive coronary artery disease and overlooking ‘milder’ nonobstructive coronary artery disease, which in itself may represent a potential missed opportunity to offer preventative treatment.^{28,29}

Limitations

Our study has a number of limitations which we should acknowledge. Although prescribing data were prospectively collected in the RAPID-CTCA trial database, neither prescription of preventative treatment nor their adjustment were prespecified outcomes. Preventative treatment was documented as therapeutic classes without the granularity of the specific drug or dose details, and they were reviewed at discharge only, for which we do not know the downstream persistence of these therapies. In addition, the RAPID-CTCA trial included a selected population of patients who were at intermediate risk with either a history of coronary artery disease, any electrocardiographic abnormalities suggesting myocardial ischemia, or cardiac troponin elevation, and we further excluded those who did not survive to discharge in this study. Our findings may not be generalizable to the broader population of patients with suspected acute coronary syndrome. Finally, given our analysis stratified by CTCA finding was *post hoc*, the results should be considered exploratory.

In conclusion, in the RAPID-CTCA trial, overall prescription of statin, renin-angiotensin system blocker, and beta-blocker therapies rose from randomization to discharge in patients with suspected acute coronary syndrome, in whom early CTCA further raised prescription of P2Y₁₂ receptor antagonist-based and statin therapies. Anatomical characterization of coronary arteries by CTCA refined the use of preventative treatment, leading to more targeted initiation, cessation, and dose or potency alterations of these therapies.

Disclosure

We have no competing interests related to this manuscript to disclose. Katherine Oatey reports research grants from the British Heart Foundation, the Jon Moulton Charity Trust, and University of Edinburgh. Nick Curzen reports research grants from Beckman Coulter, Boston Scientific, HeartFlow, and Haemonetics; consulting fees and/or honoraria from Abbott, Boston Scientific, and Edwards Lifesciences; travel sponsorship from Abbott, Biosensors, and Edwards Lifesciences. Attila Kardos reports honoraria from the TomTec Imaging Systems. Liza Keating reports research grants from the Medical Research Council Developmental Pathway Funding Scheme and the Royal College of Emergency Medicine. Robert F Storey reports research grants from AstraZeneca, Cytosorbents, and GlyCardial Diagnostics; consulting fees and/or honoraria from Alfasigma, Alnylam Pharmaceuticals, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Chiesi, CSL Behring, Cytosorbents, Daiichi-Sankyo, GlyCardial Diagnostics, Hengrui, Idorsia, Intas Pharmaceuticals, Novartis, Pfizer, PhaseBio, Sanofi, and Thromboserin. Carl Roobottom reports honoraria from GE HealthCare.

CRediT authorship contribution statement

Kang-Ling Wang: Conceptualization, Formal analysis, Visualization, Writing – original draft. **Mohammed N. Meah:** Conceptualization, Writing – original draft. **Anda Bularga:** Conceptualization, Writing – review & editing. **Katherine Oatey:** Project administration, Writing – review & editing. **Rachel O'Brien:** Data curation, Writing – review & editing. **Jason E. Smith:** Investigation, Writing – review & editing. **Nick Curzen:** Investigation, Writing – review & editing. **Attila Kardos:** Investigation, Writing – review & editing. **Liza Keating:** Investigation, Writing – review & editing. **Dirk Felmeden:** Investigation, Writing – review & editing. **Robert F. Storey:** Investigation, Writing – review & editing. **Steve Goodacre:** Investigation, Writing – review & editing. **Carl Roobottom:** Investigation, Writing – review & editing. **David E. Newby:** Funding acquisition, Supervision, Methodology, Writing – original draft. **Alasdair J. Gray:**

Funding acquisition, Supervision, Methodology, Writing – review & editing.

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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.2023.09.003](https://doi.org/10.1016/j.ahj.2023.09.003).

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