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Benefit-Risk of Colchicine and Spironolactone in Acute Myocardial Infarction: A Prespecified Generalized Pairwise Comparisons Analysis of the CLEAR Trial

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Abstract

Background: Composite outcomes in cardiovascular trials often group events of unequal clinical importance, and conventional analyses may obscure treatment trade-offs. Generalized pairwise comparisons (GPC), expressed as a win ratio, allow for hierarchical ranking of events and incorporation of recurrent outcomes, providing a potentially more intuitive assessment of benefit–risk.

Methods: In a prespecified exploratory analysis of the 2×2 factorial, randomized CLEAR trial (7,062 patients within 72 hours of acute myocardial infarction (MI) and percutaneous coronary intervention), we applied both time-to-first and recurrent-event GPC to reassess low-dose colchicine (0.5 mg daily) and spironolactone (25 mg daily) versus placebo. For the colchicine comparison, the hierarchical benefit–risk outcome included all-cause death, stroke, recurrent MI, unplanned ischemia-driven revascularization, serious infection, or diarrhea. For the spironolactone comparison, the outcome included all-cause death, stroke, MI, new or worsening heart failure, significant ventricular arrhythmia, hyperkalemia, or gynecomastia/gynecodynia. GPC results were compared with Cox, logistic, and Andersen–Gill models.

Results: For colchicine, the time-to-first event GPC showed a 12% lower proportional win rate compared to placebo (WR 0.88, 95% CI 0.79–0.98; win difference –2.10%, 95% CI –3.84 to –0.37), driven largely by excess diarrhea. For spironolactone, patients experienced a 14% lower win rate (WR 0.86, 95% CI 0.75–0.99; win difference –1.46%, 95% CI –2.84 to –0.08), largely attributable to gynecomastia and hyperkalemia. Conventional statistical approaches yielded concordant results. Across both interventions, higher-order efficacy outcomes (death, MI, stroke, heart failure) showed no benefit.

Conclusion: In post-MI patients, both low-dose colchicine and spironolactone demonstrated disadvantageous benefit–risk profiles, reinforcing that neither agent should be used routinely. This prespecified application of GPC provided results consistent with traditional methods but offered a clinically intuitive framework for interpreting composite outcomes.

What is already known on this topic:

The CLEAR trial reported no benefit and increased adverse effects with colchicine or spironolactone after myocardial infarction. However, it is unclear whether the conventional time-to-first event analyses missed important differences in recurrent events or the overall balance of efficacy and harm.

What this study adds:

In a prespecified analysis of the CLEAR trial, we applied generalized pairwise comparisons (GPC), a methodology that accounts for hierarchical clinical priorities and recurrent events. Both colchicine and spironolactone demonstrated disadvantageous benefit–risk profiles compared with placebo, driven by adverse events without efficacy gains.

How this study might affect research, practice, or policy:

Clinically, the findings reinforce that neither colchicine nor spironolactone should be used routinely post-MI. Methodologically, this study demonstrates how prespecified GPC analyses can strengthen trial interpretation, clarify benefit–risk trade-offs, and inform the design of future cardiovascular trials.

Abbreviations and acronyms

GEE	Generalized estimating equations
GPC	Generalized pairwise comparisons
HF	Heart failure
IDR	Ischemia driven revascularization
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
NSTEMI	Non-ST-elevation myocardial infarction
STEMI	ST-elevation myocardial infarction
WR	Win ratio

Introduction

The Colchicine and Spironolactone in Patients with Myocardial Infarction (CLEAR) trial was a 2 x 2 factorial randomized controlled trial of low-dose colchicine 0.5 mg daily versus placebo and spironolactone 25 mg daily versus placebo in 7,062 post-myocardial infarction (MI) participants who were within 72 hours of the index percutaneous coronary intervention (PCI).[1] Despite lowering CRP levels at 3 months compared to placebo, colchicine was not associated with a reduction in the primary composite outcome of cardiovascular death, recurrent MI, stroke, or unplanned ischemia-driven revascularization (IDR) at a median follow-up of 3 years (hazard ratio (HR) adjusted for competing risks 0.99; 95% confidence interval (CI) 0.85 – 1.16; p = 0.93).[2] Colchicine was, however, associated with a significant increase in diarrhea (10.2% versus 6.6%, p < 0.001). Similarly, compared to placebo, spironolactone did not decrease the risk for both co-primary outcomes: (1) total cardiovascular deaths or new or worsening heart failure (HF) (HR adjusted for competing risks 0.91, 95%CI 0.69 – 1.21, p = 0.51), (2) cardiovascular death, myocardial infarction, stroke or new or worsening HF (HR adjusted for competing risks 0.96, 95%CI 0.81 – 1.13, p = 0.60).[3] However, spironolactone did increase hyperkalemia, leading to discontinuation of the trial regimen (1.1% versus 0.6%, p = 0.01) and gynecomastia (2.3% versus 0.5%, p < 0.001).

The reporting of time-to-first event composite outcomes emphasizes each patient's first event but does not distinguish between the importance of events comprising the composite, nor does it consider recurrent events. Patients frequently experience multiple recurrent events before death, potentially leading to a skewed perception of the efficacy and harm of the tested intervention.[4, 5] Generalized pairwise comparisons (GPC) is an analytic method for

randomized controlled trials that defines a hierarchy of clinical importance of components of the composite outcome and can accommodate recurrent events.[4, 6, 7]

Therefore, this analysis aimed to compare the differences between time-to-first-event GPC and recurrent GPC analyses with conventional statistical approaches for broad benefit-risk outcomes in both factorials of the CLEAR randomized trial.[8]

Methods

Study Organization and Study Population

The CLEAR trial was a 2 x 2 factorial, international, investigator-initiated, blinded, multicenter, placebo-controlled trial of low-dose colchicine and spironolactone in patients with acute myocardial infarction. A detailed description of the study design has been previously published, and the protocol is available in the **online supplemental file 1**.[1] In brief, patients experiencing a ST-elevation myocardial infarction (STEMI) or high-risk non-ST-elevation myocardial infarction (NSTEMI) undergoing percutaneous coronary intervention (PCI) were randomized within 72 hours of index PCI in a factorial 1:1:1:1 allocation to receive colchicine/spironolactone, colchicine/spironolactone placebo, colchicine placebo/spironolactone or colchicine placebo/spironolactone placebo. Randomization was stratified by MI type and study center. The Population Health Research Institute, located in Hamilton, Canada, was the coordinating center for the trial. The ethics committee of each participating center and the relevant national regulatory authorities approved the original trial. No additional ethics committee or institutional review board clearance was required for this analysis.

Interventions

Study drugs were colchicine tablets of 0.5mg and spironolactone tablets of 25mg once daily orally with matching placebos. Colchicine dosage was initially weight-based, with patients weighing ≥ 70 kg receiving twice-a-day dosing and those < 70 kg receiving once-a-day dosing for the first 3 months. However, after the COLCOT trial demonstrated efficacy with once-daily dosing and a blinded interim analysis revealed higher-than-expected drug discontinuation rates, the steering committee adopted the once-daily regimen throughout the treatment period, regardless of weight, in September 2020.[9]

Outcomes

For the present analysis, we pre-specified four composite outcomes for the colchicine factorial and four composite outcomes for the spironolactone factorial. Our primary objective was to determine the benefit-risk profiles for both factorials.

For the colchicine factorial, outcomes were defined hierarchically as follows: (1) benefit-risk as the composite of all-cause death, stroke, MI, unplanned IDR, serious infection or diarrhea, (2) primary efficacy as the composite of cardiovascular death, stroke, MI, or unplanned IDR, (3) modified primary efficacy as the composite of stroke, cardiovascular death, MI, or unplanned IDR, and (4) 3-point major adverse cardiovascular events (MACE) as the composite of cardiovascular death, stroke or MI.

For the spironolactone factorial, outcomes were also defined hierarchically as follows: (1) benefit-risk as all-cause death, stroke, MI, new or worsening HF, significant ventricular arrythmia, hyperkalemia leading to drug discontinuation or gynecomastia/gynecodynia, (2) co-primary 1 as the composite of cardiovascular death or new or worsening HF, (3) co-primary 2 as

the composite of cardiovascular death, stroke, MI, or new or worsening HF, and (4) modified co-primary 2 as the composite of cardiovascular death, stroke, new or worsening HF or MI.

The outcomes were pre-specified before the investigators were unblinded to the initial trial results, and are based on the original trial outcome definitions and expert opinion.[2, 3] The modified primary efficacy and modified co-primary 2 outcomes for colchicine and spironolactone, respectively, were created to explore whether changing the hierarchy would modify the GPC results. Stroke was placed before myocardial infarction for the benefit-risk outcomes, given that many patients and clinicians may view stroke as being worse than a myocardial infarction.[10] Significant ventricular arrythmia was added to the spironolactone factorial benefit-risk outcome, as previous trial data suggested some benefit regarding sudden cardiac death outcomes.[11, 12] For reference, individual efficacy components of composite outcomes for each factorial were analyzed using a Cox proportional hazards model, stratified by the opposite component of the factorial design. Adverse events were compared using chi-square tests. Outcome definitions have been previously described.[1]

Statistical analysis

Using the intention-to-treat population, we first calculated the number of patients with an event (first event) and the total number of events (first plus recurrent) for each outcome and each factorial. We employed a bundling approach for the recurrent cardiovascular events of MI, stroke, and unplanned IDR, meaning that any of these events occurring within 48 hours of cardiovascular death was excluded, and only one non-fatal event was counted per 48-hour period.[13] We then used the GPC methodology to calculate win ratio (WR) statistics.[4, 6] All patients in the treatment group for each factorial were compared to those in the control group for

the occurrence of individual components of the composite outcomes in the predefined hierarchical order. If the pairwise comparison did not result in a win for the first component of the composite, a tie was declared, and the analysis moved on to the next event in the hierarchy. If only one patient of the pair experienced an adverse event, the patient without the event was declared the winner. When both patients of the pair experienced an event, the patient who experienced the event last, considering time from randomization, was declared the winner. This process continued until all events that comprised the composite outcome were exhausted. The WR was calculated as the number of wins divided by the number of losses and was accompanied by a 95% confidence interval. A WR greater than 1 indicated an effect favouring the intervention over the control. Given the importance of absolute effects, we calculated the win difference, defined as the percent wins minus the percent losses for both comparisons. We also calculated win odds for comparison.

Outcomes were first analyzed using first events as the primary analysis and, subsequently, using recurrent events. When using the GPC methodology for recurrent events, the comparison for each individual component of the hierarchy was based on the number of events, with the winner having the fewest number of events. If pairs had the same number of events for that specific individual component of the hierarchy, the patient who had their last event the latest, considering time from randomization, was considered the winner. The bundling approach was used to decrease statistical noise and increase model performance in cases where recurrent MI, unplanned IDR and cardiovascular death could be double or triple-counted if occurring during the same 48 hours.

For comparison with first-event and recurrent win-ratio analyses, each outcome was analyzed as time-to-event using a Cox proportional hazard model and recurrent events using the

Andersen-Gill model.[5] For easier qualitative comparison of results, we presented the results of these analyses as 1/HR.[14] Survival curves and interaction testing between log(time) and treatment were performed to detect violation of the proportional hazards assumption (**Figure S1**, **Table S1**). The proportional hazards assumption was not met for the colchicine benefit-risk outcome ($p < 0.01$ for the time-by-treatment interaction). Therefore, for this outcome, we used logistic regression with follow-up time included as a log-transformed offset variable in place of the Cox model and a logistic generalized estimating equations (GEE) in place of the Andersen-Gill model.[15] These results were presented as 1/OR. We also used the Fine-Gray subdistribution hazard model for the time-to-first event analysis to account for the competing risk of death from non-cardiovascular causes for outcomes that included death from cardiovascular causes.

All analyses were stratified by the opposite component of the factorial design, for both conventional and GPC analyses. A two-sided p-value < 0.05 was considered statistically significant. We did not adjust for multiplicity. All analyses were performed using R, version 4.2.3.

Patient and public involvement

We did not involve patients or the public in our research design, conduct, reporting, or dissemination plans.

Results

Patient baseline characteristics have been previously reported.[2, 3] A total of 7,062 patients were randomized with a median follow-up of three years. The mean age was 61 years,

with approximately 20% of the participants being of female sex, 95% presenting with a STEMI at enrollment and 99% presenting as Killip class 1. At the end of the follow-up, there was an approximately 26% study drug discontinuation rate.

Table 1 summarizes the number of participants with an event and recurrent events (respecting the 48-hour bundling approach) for both factorials and by treatment allocation. The number of first and recurrent benefit-risk events for participants randomized to colchicine was 703 and 835, respectively, and was 632 and 758, respectively, for those randomized to placebo. Participants randomized to spironolactone experienced 442 and 512 first and recurrent benefit-risk events, respectively, while those randomized to placebo experienced 379 and 428 events, respectively. **Table 2** provides the results of the time-to-event and recurrent event GPC, compared to more traditional statistical approaches. **Table 3** demonstrates the win differences for the time-to-event GPC analysis. **Figures 1 and 2** highlight the distributions of wins, ties, and losses as well as win difference at each level of the hierarchy for each factorial's benefit-risk outcome.

Individual components of the composite outcomes are available in **Table S2-S3**. The win odds results are demonstrated in **Table S4.** The competing risk analysis results are presented in **Table S5**.

Colchicine factorial

For the benefit-risk outcome of the colchicine factorial using the time-to-first event GPC, for any randomly chosen pair of patients (one on colchicine and the other on placebo) for whom there was no tie, the proportional win rate was 12% lower for patients randomized to colchicine (WR 0.88, 95% CI 0.79, 0.98, p = 0.02). In absolute terms, this resulted in a win difference of -

2.10% (95% CI -3.84%, -0.37%). While minor win differences existed between the first five events of the hierarchy, the most considerable win difference was for the diarrhea component. The logistic regression and logistic GEE models with effect estimates expressed as 1/OR gave similar results to both time-to-event and recurrent win ratio models. For the primary efficacy, modified primary efficacy, and 3-point MACE outcomes, effect estimates were all similarly close to the null for all analytical models.

Spironolactone factorial

For the benefit-risk outcome of the spironolactone factorial using the time-to-first event GPC, the proportional win rate was 14% lower for patients randomized to spironolactone (WR 0.86, 95% CI 0.75, 0.99, p = 0.04). The win difference was -1.46% (95% CI -2.84%, -0.08%). Similarly to the colchicine factorial, the largest win difference occurred for the final event of the hierarchy, which was gynecomastia/gynecodynia. All other models provided comparable effect estimates for the benefit-risk outcome. For the co-primary 1, co-primary 2 and modified co-primary 2 outcomes, all four models provided similar effect estimates, reflecting no difference between patients randomized to spironolactone versus placebo.

Discussion

Key Findings

Our re-analysis of the CLEAR data sheds important insights from a clinical and methodological standpoint. When defining the benefit-risk outcome as a broad composite encompassing the most important and relevant events, both low-dose colchicine and spironolactone were shown to be disadvantageous compared to placebo in post-MI patients.

These findings were consistent when evaluated by both conventional and novel methodology.

Comparison to prior evidence

GPC methodology is used frequently as an analytical method to reevaluate the results of previously published trials.[16] Our results are concordant with multiple previous reanalyses of large randomized trials, where GPC methodology provides qualitatively similar results as more conventional statistical techniques.[14, 17, 18] Given the statistical properties of GPC methodology, when the proportional hazards assumption holds, the WR resembles the inverse of the HR.[7] As the proportion hazards assumption was not violated except for the benefit-risk of the colchicine factorial, the results for the time-to-first event analyses were comparable. Time-to-worst event GPC analysis can be more clinically intuitive than a time-to-first event analysis. This can be observed in trials of longer duration, where events become more severe in GPC, as compared to time-to-first event, in which the first event remains the counted event, regardless of its severity. Some trials using GPC methodology have shown no difference between therapies for important clinical outcomes, but leverage quantitative surrogate or quality-of-life outcomes to differentiate treatment arms.[16] Nevertheless, GPC methodology with quantitative outcomes has been used to obtain regulatory approval.[19]

Recurrent event analyses can better represent the total disease burden, unlike time-to-first event analyses, which only consider the first event.[5] Analyses that include repeat events are used, especially in heart failure trials, where multiple non-fatal events tend to recur.[20] The results for both recurrent event and time-to-first event analyses were similar, which is most likely explained by the small fraction of recurrent events.

Implications for clinical practice and research

Consistent with the main CLEAR trial results, our current analysis does not support the routine use of colchicine and spironolactone in a largely Killip class 1 STEMI population who underwent percutaneous revascularization.[2, 3] The benefit-risk outcome results reflect a lack of efficacy for both colchicine and spironolactone, with both having a disadvantageous adverse effect profile compared to placebo in the intention-to-treat population.

In theory, conventional analytical approaches to composite outcomes can be misleading, giving equal importance to all components and thereby inflating the importance of less significant components.[16] Hierarchical composites highlight the clinical priorities among components and may better illustrate the treatment effect. However, each component of GPC is weighted equally, and, like conventional composite outcomes, it could be driven by the least clinically meaningful but most frequent component, rather than the highest-priority, infrequent event.[6] For both the colchicine and spironolactone factorials, the win ratio statistics were mainly driven by the least important components, whereas higher-ranking components were similar between groups. Luo et al. have described a methodology that weights wins and losses according to when they occur, so that a win occurring later can be weighted more than a win occurring earlier.[21] The hierarchical ranking of outcomes is already subjective; therefore, additional weighing by perceived clinical importance would introduce another layer of subjectivity and would be challenging to implement and interpret.[21] Conclusions regarding composite outcomes, whether analyzed by conventional methods or GPC, should take into consideration the importance of each outcome and the directionality of the effect estimates to avoid misleading statements.[7, 22] Furthermore, benefit-risk outcomes may be viewed as a measure of effectiveness rather than efficacy, given that lower importance adverse events may

result in treatment discontinuation, therefore, further decreasing the likelihood of demonstrating the benefit of a potentially efficacious treatment.

Careful consideration is required when choosing GPC methodology over more conventional approaches. The limitations of GPC include less intuitive interpretation of results compared to relative risks, subjectivity in the order of the hierarchy, and complex power calculations.[6] Our analysis suggests that choosing a recurrent GPC analytical framework or other recurrent event frameworks may be better guided by the inclination to study total disease burden rather than by pursuing statistical efficiency. Demonstrating a treatment effect on the total disease burden may be more clinically intuitive than only demonstrating differences in time-to-first event in HF populations. [20]

Limitations

Our manuscript has several limitations. First, our primary time-to-first event GPC analysis for the risk-benefit outcome of both colchicine and spironolactone had a high proportion of ties, which may have skewed the effect estimate away from the null.[6] However, we calculated win differences to allow insights into each component and win odds, which may be less affected by ties.[16] Second, while the GPC method can be leveraged to hierarchically rank components of composite outcomes, conventional analyses using time-to-first event (Cox proportional hazards model or logistic regression models) and recurrent event (Andersen-Gill or logistic GEE models) give equal weight to all components of the composite outcome. Therefore, caution is advised when interpreting the conventional analyses for the benefit-risk outcomes of both factorials, given the discrepancy in outcome importance, such as death and diarrhea or gynecomastia/gynecodynia. Additionally, careful interpretation is also required for hierarchical

outcomes when benefit-risk outcomes go in opposite directions, vary in terms of severity and are only experienced by a minority of patients. Lastly, given the lack of adjustment for multiplicity and the number of analyses, these results should be considered exploratory, given the risk of type 1 error.

Conclusions

In the CLEAR trial population of post-MI patients treated with PCI, participants randomized to low-dose colchicine experienced a 12% lower win rate for the broad benefit-risk outcome compared to placebo. Similarly, participants randomized to spironolactone experienced a 14% lower win rate for the broad benefit-risk outcome. These results were primarily attributed to the lack of benefit on key efficacy outcomes and the less severe, disadvantageous side effect profiles of the study drugs. Therefore, the GPC analysis does not support the routine use of either low-dose colchicine or spironolactone in post-MI patients.

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Contributorship

All authors have contributed to the planning, conduct and reporting of the CLEAR trial and the current manuscript. Marc-André d'Entremont is the guarantor of the overall content.

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Figure legends

Figure 1. Distribution of wins and ties for each of the colchicine versus placebo paired comparisons at each level of the hierarchy for the colchicine benefit-risk outcome; CI, Confidence Interval; IDR, ischemia-driven revascularization; MI, Myocardial infarction

Figure 2. Distribution of wins and ties for each of the spironolactone versus placebo paired comparisons at each level of the hierarchy for the spironolactone benefit-risk outcome; CI, Confidence interval; Gynecomastia, Gynecomastia/Gynecodynia; HF, New or worsening heart failure; Hyperkalemia, Hyperkalemia leading to drug discontinuation; MI, Myocardial infarction, VT/VF, Significant ventricular arrythmia.

Table 1. Number of first and recurrent events among patients randomized to colchicine versus placebo and spironolactone versus placebo in the CLEAR trial.

Composite event	**Colchicine (n = 3528)**		**Placebo (n = 3534)**	
	Patients with an event	Number of events	Patients with an event	Number of events
Benefit-risk (All-cause death, stroke, MI, unplanned IDR, serious infection or diarrhea)	703	835	632	758
Primary efficacy (CV death, stroke, MI, or unplanned IDR)	322	371	327	387
Modified primary efficacy (Stroke, CV death, MI, or unplanned IDR)	322	371	327	387
3-point MACE (CV death, stroke or MI)	241	283	250	286
Composite event	**Spironolactone (n = 3537)**		**Placebo (n = 3525)**	
	Patients with an event	Number of events	Patients with an event	Number of events
Benefit-risk (All-cause death, stroke, MI, new or worsening HF, significant ventricular arrythmia, hyperkalemia, gynecomastia/gynecodynia)	442	512	379	428
Co-primary 1 (CV death, new or worsening HF)	158	182	176	215
Co-primary 2 (CV death, stroke, MI, or new or worsening HF)	280	357	294	366
Modified co-primary 2 (CV death, stroke, new or worsening HF, or MI)	280	357	294	366

CV, Cardiovascular; HF, Heart failure; IDR, Ischemia-driven revascularization; MACE; Major adverse cardiovascular events; MI, Myocardial infarction

Table 2. Comparison of GPC versus Cox or logistic regression models for time-to-first event analysis and GPC versus Andersen-Gill or GEE models for recurrent events

Composite event	Time-to-first event		Recurrent event	
	Win ratio (95% CI)	Cox proportional hazards model 1/HR or logistic regression 1/OR[1] (95% CI)	Win ratio (95% CI)	Andersen-Gill 1/HR or logistic GEE model 1/OR[2] (95% CI)
Colchicine				
Benefit-risk (All-cause death, stroke, MI, unplanned IDR, serious infection or diarrhea)	0.88 (0.79, 0.98)	0.83 (0.73, 0.94)	0.88 (0.79, 0.98)	0.88 (0.76, 1.02)
Primary efficacy (CV death, stroke, MI, or unplanned IDR)	1.00 (0.85, 1.17)	1.02 (0.87, 1.18)	1.00 (0.85, 1.17)	1.04 (0.88, 1.24)
Modified primary efficacy (Stroke, CV death, MI, or unplanned IDR)	1.00 (0.85, 1.17)	1.02 (0.87, 1.18)	1.00 (0.85, 1.17)	1.04 (0.88, 1.24)
3-point MACE (CV death, stroke or MI)	1.00 (0.83, 1.20)	1.04 (0.87, 1.24)	1.00 (0.83, 1.20)	1.01 (0.84, 1.23)
Spironolactone				
Benefit-risk (All-cause death, stroke, MI, new or worsening HF, significant ventricular arrythmia, hyperkalemia, gynecomastia/gynecodynia)	0.86 (0.75, 0.99)	0.85 (0.74, 0.97)	0.83 (0.72, 0.95)	0.83 (0.72, 0.99)
Co-primary 1 (CV death, new or worsening HF)	1.12 (0.90, 1.40)	1.12 (0.90, 1.39)	1.12 (0.90, 1.40)	1.18 (0.93, 1.50)
Co-primary 2 (CV death, stroke, MI, or new or worsening HF)	1.06 (0.90, 1.26)	1.05 (0.89, 1.24)	1.06 (0.90, 1.26)	1.03 (0.86, 1.23)
Modified co-primary 2 (CV death, stroke, new or worsening HF, or MI)	1.07 (0.90, 1.26)	1.05 (0.89, 1.24)	1.06 (0.90, 1.26)	1.03 (0.86, 1.23)

CI, Confidence interval; CV, Cardiovascular; GEE, Generalized estimating equations; GPC, Generalized pairwise comparison; HF, Heart failure; HR; Hazard ratio; IDR, Ischemia-driven revascularization; MACE, Major adverse cardiovascular events; MI, Myocardial infarction; OR, Odds ratio

[1] Logistic regression with follow-up time as a log-transformed offset variable was used for the colchicine benefit-risk given that the assumption of proportional hazards was violated

[2] Logistic generalized estimating equations were used for the colchicine benefit-risk given that the assumption of proportional hazards was violated

Table 3. Win difference for time-to-first event analyses for both factorials

Composite event	Win difference, % (95% CI)
Colchicine	
Benefit-risk (All-cause death, stroke, MI, unplanned IDR, serious infection or diarrhea)	-2.10 (-3.84, -0.37)
Primary efficacy (CV death, stroke, MI, or unplanned IDR)	-0.02 (-1.25, 1.20)
Modified primary efficacy (Stroke, CV death, MI, or unplanned IDR)	-0.03 (-1.26, 1.19)
3-point MACE (CV death, stroke or MI)	0.00 (-1.08, 1.08)
Spironolactone	
Benefit-Risk (All-cause death, stroke, MI, new or worsening HF, significant ventricular arrythmia, hyperkalemia, gynecomastia/gynecodynia)	-1.46 (-2.84, -0.08)
Co-primary 1 (CV death, new or worsening HF)	0.46 (-0.45, 1.37)
Co-primary 2 (CV death, stroke, MI, or new or worsening HF)	0.42 (-0.74, 1.58)
Modified co-primary 2 (CV death, stroke, new or worsening HF, or MI)	0.44 (-0.73,1.61)

CI, Confidence interval; CV, Cardiovascular; HF, Heart failure; HR; Hazard ratio; IDR, Ischemia-driven revascularization; MACE, Major adverse cardiovascular events; MI, Myocardial infarction