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Pharmacogenomics of the Efficacy and Safety of Colchicine in COLCOT

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Abstract:

Background - The randomized, placebo-controlled COLchicine Cardiovascular Outcomes Trial (COLCOT) has shown the benefits of colchicine 0.5 mg daily to lower the rate of ischemic cardiovascular events in patients with a recent myocardial infarction. Here, we conducted a post-hoc pharmacogenomic study of COLCOT with the aim to identify genetic predictors of the efficacy and safety of treatment with colchicine.

Methods - There were 1522 participants of European descent from the COLCOT trial available for the pharmacogenomic study of COLCOT trial. The pharmacogenomic study's primary cardiovascular (CV) endpoint was defined as for the main trial, as time to first occurrence of CV death, resuscitated cardiac arrest, myocardial infarction, stroke or urgent hospitalization for angina requiring coronary revascularization. The safety endpoint was time to the first report of gastrointestinal events. Patients' DNA was genotyped using the Illumina Global Screening array followed by imputation. We performed a genome-wide association study (GWAS) in colchicine-treated patients.

Results - None of the genetic variants passed the GWAS significance threshold for the primary CV endpoint conducted in 702 patients in the colchicine arm who were compliant to medication. The GWAS for gastrointestinal events was conducted in all 767 patients in the colchicine arm and found two significant association signals, one with lead variant rs6916345 (hazard ratio (HR)=1.89, 95% confidence interval (CI) 1.52-2.35, $P=7.41 \times 10^{-9}$) in a locus which colocalizes with Crohn's disease, and one with lead variant rs74795203 (HR= 2.51, 95% CI 1.82-3.47; $P=2.70 \times 10^{-8}$), an intronic variant in gene *SEPHSI*. The interaction terms between the genetic variants and treatment with colchicine versus placebo were significant.

Conclusions - We found two genomic regions associated with gastrointestinal events in patients treated with colchicine. Those findings will benefit from replication to confirm that some patients may have genetic predispositions to lower tolerability of treatment with colchicine.

Key words: pharmacogenetics; acute coronary syndrome; COLCOT; colchicine; gastrointestinal disorder

Nonstandard Abbreviations and Acronyms

ABCB1: ATP Binding Cassette Subfamily B Member 1 gene

BMI: body mass index

CABG: coronary artery bypass graft

CI: Confidence interval

COLCOT: COLchicine Cardiovascular Outcomes Trial

CV: Cardiovascular

CYP3A4: Cytochrome P450 Family 3 Subfamily A Member 4

EA: effect allele

EAF: effect allele frequency

GWAS: Genome-wide association study

HAUS6: HAUS Augmin Like Complex Subunit 6 gene

HR: Hazard ratio

MI: Myocardial infarction

PCI: percutaneous coronary intervention

SAXO1: Stabilizer of axonemal microtubules 1 gene

SEPHS1: Selenophosphate synthetase 1 gene



Circulation: Genomic and Precision Medicine

Introduction

Inflammation plays an important role in atherosclerosis and in processes leading to and following a myocardial infarction (MI). The COLchicine Cardiovascular Outcomes Trial (COLCOT) has recently shown the benefits of the anti-inflammatory medication colchicine in reducing the rate of ischemic cardiovascular events in 4745 patients included within 30 days after MI.¹ The study's primary endpoint consisting of time to first occurrence of cardiovascular (CV) death, resuscitated cardiac arrest, nonfatal MI, non-fatal stroke, or urgent hospitalization

for angina requiring coronary revascularization was reduced by 23% by low-dose colchicine as compared to placebo after a median follow-up of 23 months.¹

Considering that patients receive long-term treatment with multiple drugs after a myocardial infarction, genomics can help identify patients more or less unlikely to derive benefits to decrease polypharmacy. Given the effects of colchicine on tubulin and multiple inflammatory pathways^{2,3}, the identification of genes associated with clinical outcomes can provide insights into the underlying mechanisms responsible for its benefits in patients with coronary artery disease. Similarly, genes linked to adverse effects may offer clues to their pathophysiology. Here, we present the post-hoc pharmacogenomic study of COLCOT in the subgroup of participants who took part in the optional genetic substudy, with the aim to identify genetic predictors of the efficacy and safety of treatment with colchicine.

Methods

The data underlying this article cannot be shared publicly to preserve the privacy of study participants, however, the data are available from the corresponding authors upon reasonable requests. The analytic methods and study materials may be made available to other researchers for purposes of reproducing the results or replicating the procedure. Summary statistics are available publicly for download and visualisation via PheWEB⁴ at statgen.org/pheweb/colcot. The COLCOT clinical trial was registered at www.clinicaltrials.gov under the unique identifier NCT02551094. The study protocol was approved by the Montreal Heart Institute research ethics committee and complies with the Declaration of Helsinki. Written informed consent was obtained from all participating subjects. Full Methods are available in the Data Supplement of the article.

Results

There were 1522 participants included in the pharmacogenomic analysis of COLCOT of which 767 were randomized to colchicine and 755 to placebo (Supplemental Figure I). The baseline characteristics of patients according to the study treatment groups are shown in Table 1. The mean age of participants was 60.9 years and 81.3% were male. The COLCOT study primary CV endpoint occurred in 6.2% of patients who consented to the pharmacogenomic substudy, as compared to 6.3% of those in the main trial ($P=0.86$) (Supplemental Table I). Gastrointestinal adverse events occurred in 23.4% of the pharmacogenomic study population, as compared to 17.6% of the COLCOT trial participants ($P=1.8\times 10^{-7}$).

Genetic determinants of cardiovascular efficacy with colchicine



The pharmacogenomic analyses of the primary CV efficacy endpoint were limited to the 702 participants randomized to colchicine who used the study drug with at least 80% compliance in the first 6 months of treatment. Of those, 39 patients had an event. The prespecified analysis for the ATP binding cassette subfamily B member 1 gene (*ABCB1*) variant rs1045642 and the Cytochrome P450 family 3 subfamily A member 4 (*CYP3A4*) metaboliser phenotype were not associated with the primary CV efficacy endpoint ($P=0.77$ and $P=0.91$, respectively), and none of the tested genetic variants passed the genome-wide association study (GWAS) significance threshold ($P<5\times 10^{-8}$) (Supplemental Figure II.a). However, the GWAS analysis had limited power and negative results should be interpreted with care. The sex-stratified GWAS with 576 male participants also did not provide any GWAS-significant findings (Supplemental Figure II.b), however there was some interest for the top signal on chromosome 9 at rs10811106 ($P=5.8\times 10^{-8}$) near the *SAXO1* gene (also known as *FAM154A*), as it encodes the stabilizer of axonemal microtubules 1 (Supplemental Figure III.b).

Genetic determinants of gastrointestinal adverse events with colchicine

There were 767 participants randomized to colchicine who were included in the genetic analyses for gastrointestinal adverse events, of those, 187 had a gastrointestinal event. The *ABCB1* rs1045642 variant and the CYP3A4 metaboliser phenotype were not associated with gastrointestinal adverse events ($P=0.97$ and $P=0.31$ respectively). We found 22 genetic variants significantly associated with gastrointestinal events at 2 loci located on chromosomes 6 and 10 (Figure 1). The most significant association on chromosome 6 was the intergenic variant rs6916345 ($P=7.41\times 10^{-9}$). When conditioning on rs6916345, no additional genetic variants remained significant at $P<5\times 10^{-8}$ in the region and rs6916345 had the highest probability of being causal by CAVIAR analysis (Data Supplement). The minor allele (A) was associated with gastrointestinal events in the colchicine group (hazard ratio (HR)=1.89, 95% confidence interval (CI) 1.52-2.35, $P=7.41\times 10^{-9}$) with an estimated effect in the placebo group of HR=1.30 (95% CI 1.04-1.62; $P=0.02$). The effect appeared to be mostly driven by the occurrence of diarrhea (Supplemental Table II). The interaction term between rs6916345 and colchicine treatment was significant ($P=2.96\times 10^{-8}$) (Table 2). Individuals with the AA genotype represented 25% of the trial population. Gastrointestinal adverse events were reported by 36.9% of AA patients in the colchicine group compared to 18.6% in the placebo group (HR=2.42, 95% CI 1.57-3.72, $P=5.77\times 10^{-5}$) (Table 3). We found evidence of colocalization of the locus with Crohn's disease (Supplemental material, Supplemental Figure V). The risk allele (A) at rs6916345 was previously associated with Crohn's disease (odds ratio = 1.07, $P = 3.1\times 10^{-5}$).⁵

The most significant association at the chromosome 10 locus was at rs10128117 located in intron 2 of the selenophosphate synthetase 1 gene (*SEPHS1*). However, because this variant is triallelic and was imputed as biallelic, we report the findings based on variant, rs74795203, in

strong linkage disequilibrium, located in intron 4 of the gene (Supplemental Figure IV.b). The G allele of variant rs74795203 was associated with gastrointestinal events with a HR of 2.51 (95% CI 1.82-3.47; $P=2.70 \times 10^{-8}$) with an estimated effect in the placebo group of HR=0.71 (95% CI 0.46-1.09; $P=0.11$). The interaction term between rs74795203 and colchicine treatment was significant ($P=3.13 \times 10^{-6}$) (Table 2). When conditioning on rs10128117 or rs74795203, no additional genetic variants remained significant at $P < 5 \times 10^{-8}$. Individuals with the AG or GG genotype at rs74795203 represented 13% of the trial population. Gastrointestinal adverse events were reported by 47.1% of patients with the AG or GG genotype in the colchicine arm compared to 18.9% in the placebo arm (HR=3.98, 95% CI 2.24-7.07, $P=2.33 \times 10^{-6}$) (Table 3). The GWAS limited to 622 male participants did not identify additional association signals.



Discussion

In this pharmacogenomic study of the randomized, placebo-controlled COLCOT trial, genetic variants were found to be associated with gastrointestinal events in patients treated with colchicine, offering insights into the biological mechanisms underlying the tolerability of treatment with colchicine. Although the signal did not reach the significance threshold, we have found an interesting genetic region on chromosome 9 in the pre-specified analysis in males that is possibly associated with the CV benefits of colchicine. The locus is particularly interesting as it spans the stabilizer of axonemal microtubules 1 (*SAXOI*) gene and it colocalizes with the expression of the HAUS Augmin Like Complex Subunit 6 (*HAUS6*) gene which is involved in microtubule generation from existing microtubules and in kinetochore-microtubule attachment and central spindle formation during anaphase.⁶ The CV event risk allele at the leading variant reduces *HAUS6* expression, and it may possibly interact with the effects of colchicine on tubulin

binding and microtubule polymerization. However, replication of this locus in future cardiovascular studies with colchicine is necessary.

The genome-wide analysis of gastrointestinal adverse events found two associated regions. The first region on chromosome 6 is particularly appealing as it colocalizes with a previously identified locus for Crohn's disease.⁵ The risk allele of the lead variant at this locus was previously associated with Crohn's disease risk and with reticulocyte counts and hemoglobin concentrations, which are common extra-intestinal complication of Crohn's disease. The second genetic locus on chromosome 10 overlaps the selenophosphate synthetase 1 gene (*SEPHS1*), which encodes an enzyme that synthesizes selenophosphate from selenide and ATP. We found evidence of colocalization of the region with expression of *SEPHS1*, with correlation between the gastrointestinal disorder risk allele and lower *SEPHS1* gene expression.

Despite the relatively small proportion of participants who consented to take part in the pharmacogenomic substudy of COLCOT (32%), we have found significant and credible association signals predictive of gastrointestinal events with colchicine use. There may be volunteer bias in the pharmacogenomic subgroup compared to the main trial population, and we observed a lower occurrence of deaths, possibly attributable to the fact that not all patients were recruited into the pharmacogenomic substudy at the baseline visit. This may have contributed to reducing the statistical power for detecting genetic association signals with the primary CV endpoint which included CV death. We also noted an overrepresentation of patients who reported suffering from gastrointestinal disorders during the course of the trial from both the colchicine and the placebo arm. This could be due to correlation between patient willingness to participate and to share information on milder gastrointestinal adverse events. We do not expect that this observation had an impact on the pharmacogenomic findings with gastrointestinal

events, as the two genetic association signals identified were strong and had strong interaction effects with colchicine treatment.

Because this study was a post-hoc investigation, these results are considered as hypothesis-generating, and they will have to be replicated prior to using the information for clinical decision-making. Colchicine is used throughout the world for indications of gout, familial Mediterranean fever, pericarditis, and, since the COLCOT trial, for secondary cardiovascular prevention. There are other ongoing and planned clinical trials designed to assess the CV benefits of colchicine where it may be possible to replicate the findings if genetic material is collected. Reliance on observational studies and registries to conduct replication studies will become an option as the long-term use of colchicine for the prevention of secondary cardiovascular disease gains in popularity in the coming years. Shorter-term use of colchicine for the treatment of gout could provide useful data for replication of the genetic variants associated with gastrointestinal events.

In conclusion, in the present pharmacogenomic study of the COLCOT trial, we have found genetic variants associated with gastrointestinal events in patients treated with colchicine. Those findings will benefit from replication to confirm our observations that some patients may have genetic predispositions to lower tolerability of treatment with colchicine.

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Supplemental Material:

Supplemental Methods
 Supplemental Results
 Supplemental Tables I-IV
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References:

1. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, Pinto FJ, Ibrahim R, Gamra H, Kiwan GS, et al. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. *N Engl J Med*. 2019;381:2497-2505.
2. Ravelli RB, Gigant B, Curmi PA, Jourdain I, Lachkar S, Sobel A and Knossow M. Insight into tubulin regulation from a complex with colchicine and a stathmin-like domain. *Nature*. 2004;428:198-202.
3. Pope RM and Tschopp J. The role of interleukin-1 and the inflammasome in gout: implications for therapy. *Arthritis Rheum*. 2007;56:3183-8.
4. Gagliano Taliun SA, VandeHaar P, Boughton AP, Welch RP, Taliun D, Schmidt EM, Zhou W, Nielsen JB, Willer CJ, Lee S, et al. Exploring and visualizing large-scale genetic associations by using PheWeb. *Nat Genet*. 2020;52:550-552.
5. de Lange KM, Moutsianas L, Lee JC, Lamb CA, Luo Y, Kennedy NA, Jostins L, Rice DL, Gutierrez-Achury J, Ji SG, et al. Genome-wide association study implicates immune activation of multiple integrin genes in inflammatory bowel disease. *Nat Genet*. 2017;49:256-261.
6. Uehara R, Nozawa RS, Tomioka A, Petry S, Vale RD, Obuse C and Goshima G. The augmin complex plays a critical role in spindle microtubule generation for mitotic progression and cytokinesis in human cells. *Proc Natl Acad Sci U S A*. 2009;106:6998-7003.
7. Hitz M-P, Lemieux-Perreault L-P, Marshall C, Feroz-Zada Y, Davies R, Yang SW, Lionel AC, D'Amours G, Lemyre E and Cullum R. Correction: Rare Copy Number Variants Contribute to Congenital Left-Sided Heart Disease. *PLoS genetics*. 2013;9.
8. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, Maller J, Sklar P, de Bakker PI, Daly MJ, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet*. 2007;81:559-75.
9. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA and Reich D. Principal components analysis corrects for stratification in genome-wide association studies. *Nat Genet*. 2006;38:904-9.
10. Howie BN, Donnelly P and Marchini J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLoS genetics*. 2009;5:e1000529.



11. Howie B, Fuchsberger C, Stephens M, Marchini J and Abecasis GR. Fast and accurate genotype imputation in genome-wide association studies through pre-phasing. *Nature Genetics*. 2012;44:955-959.
12. Delaneau O, Zagury JF and Marchini J. Improved whole-chromosome phasing for disease and population genetic studies. *Nature methods*. 2013;10:5-6.
13. Whirl-Carrillo M, McDonagh EM, Hebert JM, Gong L, Sangkuhl K, Thorn CF, Altman RB and Klein TE. Pharmacogenomics knowledge for personalized medicine. *Clin Pharmacol Ther*. 2012;92:414-7.
14. L.-P. LP. genetest. 2020; <https://github.com/pgxcentre/genetest>
15. Hormozdiari F, Kostem E, Kang EY, Pasaniuc B and Eskin E. Identifying Causal Variants at Loci with Multiple Signals of Association. *Genetics*. 2014;198:497.
16. Chen W, Larrabee BR, Ovsyannikova IG, Kennedy RB, Haralambieva IH, Poland GA and Schaid DJ. Fine Mapping Causal Variants with an Approximate Bayesian Method Using Marginal Test Statistics. *Genetics*. 2015;200:719.
17. Benner C, Spencer CC, Havulinna AS, Salomaa V, Ripatti S and Pirinen M. FINEMAP: efficient variable selection using summary data from genome-wide association studies. *Bioinformatics*. 2016;32:1493-501.
18. Lemacon A, Joly Beuparlant C, Soucy P, Allen J, Easton D, Kraft P, Simard J and Droit A. VEXOR: an integrative environment for prioritization of functional variants in fine-mapping analysis. *Bioinformatics*. 2017;33:1389-1391.
19. Lemacon A, Scott-Boyer MP, Ongaro-Carcy R, Soucy P, Simard J and Droit A. DSNetwork: An Integrative Approach to Visualize Predictions of Variants' Deleteriousness. *Front Genet*. 2019;10:1349.
20. Kamat MA, Blackshaw JA, Young R, Surendran P, Burgess S, Danesh J, Butterworth AS and Staley JR. PhenoScanner V2: an expanded tool for searching human genotype-phenotype associations. *Bioinformatics*. 2019.
- 8
21. Staley JR, Blackshaw J, Kamat MA, Ellis S, Surendran P, Sun BB, Paul DS, Freitag D, Burgess S, Danesh J, et al. PhenoScanner: a database of human genotype-phenotype associations. *Bioinformatics*. 2016;32:3207-3209.
22. Deloukas P, Kanoni S, Willenborg C, Farrall M, Assimes TL, Thompson JR, Ingelsson E, Saleheen D, Erdmann J, Goldstein BA, et al. Large-scale association analysis identifies new risk loci for coronary artery disease. *Nat Genet*. 2013;45:25-33.

23. Nelson CP, Goel A, Butterworth AS, Kanoni S, Webb TR, Marouli E, Zeng L, Ntalla I, Lai FY, Hopewell JC, et al. Association analyses based on false discovery rate implicate new loci for coronary artery disease. *Nat Genet.* 2017;49:1385-1391.
24. Mahajan A, Taliun D, Thurner M, Robertson NR, Torres JM, Rayner NW, Payne AJ, Steinthorsdottir V, Scott RA, Grarup N, et al. Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. *Nat Genet.* 2018;50:1505-1513.
25. Astle WJ, Elding H, Jiang T, Allen D, Ruklisa D, Mann AL, Mead D, Bouman H, Riveros-Mckay F, Kostadima MA, et al. The Allelic Landscape of Human Blood Cell Trait Variation and Links to Common Complex Disease. *Cell.* 2016;167:1415-1429 e19.
26. Liu JZ, van Sommeren S, Huang H, Ng SC, Alberts R, Takahashi A, Ripke S, Lee JC, Jostins L, Shah T, et al. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. *Nat Genet.* 2015;47:979-986.
27. Ligthart S, Vaez A, Vosa U, Stathopoulou MG, de Vries PS, Prins BP, Van der Most PJ, Tanaka T, Naderi E, Rose LM, et al. Genome Analyses of >200,000 Individuals Identify 58 Loci for Chronic Inflammation and Highlight Pathways that Link Inflammation and Complex Disorders. *Am J Hum Genet.* 2018;103:691-706.
28. Giambartolomei C, Vukcevic D, Schadt EE, Franke L, Hingorani AD, Wallace C and Plagnol V. Bayesian test for colocalisation between pairs of genetic association studies using summary statistics. *PLoS genetics.* 2014;10:e1004383.
29. McCarthy S, Das S, Kretzschmar W, Delaneau O, Wood AR, Teumer A, Kang HM, Fuchsberger C, Danecek P, Sharp K, et al. A reference panel of 64,976 haplotypes for genotype imputation. *Nat Genet.* 2016;48:1279-83.
30. Gauderman WJ. Sample size requirements for matched case-control studies of gene-environment interaction. *Stat Med.* 2002;21:35-50.
31. Saez ME, Gonzalez-Perez A, Hernandez-Olasagarre B, Bea A, Moreno-Grau S, de Rojas I, Monte-Rubio G, Orellana A, Valero S, Comella JX, et al. Genome Wide Meta-Analysis identifies common genetic signatures shared by heart function and Alzheimer's disease. *Sci Rep.* 2019;9:16665.
32. Ernst J and Kellis M. Chromatin-state discovery and genome annotation with ChromHMM. *Nat Protoc.* 2017;12:2478-2492.
33. Yeh MM, Bosch DE and Daoud SS. Role of hepatocyte nuclear factor 4-alpha in gastrointestinal and liver diseases. *World J Gastroenterol.* 2019;25:4074-4091
34. Burdin DV, Kolobov AA, Brocker C, Soshnev AA, Samusik N, Demyanov AV, Brilloff S, Jarzewska N, Martens-Lobenhoffer J, Mieth M, et al. Diabetes-linked transcription factor

HNF4alpha regulates metabolism of endogenous methylarginines and beta-aminoisobutyric acid by controlling expression of alanine-glyoxylate aminotransferase 2. *Sci Rep.* 2016;6:35503.

35. Moller AM, Dalgaard LT, Ambye L, Hansen L, Schmitz O, Hansen T and Pedersen O. A novel Phe75fsdelT mutation in the hepatocyte nuclear factor-4alpha gene in a Danish pedigree with maturity-onset diabetes of the young. *J Clin Endocrinol Metab.* 1999;84:367-9.

36. Marcil V, Sinnott D, Seidman E, Boudreau F, Gendron FP, Beaulieu JF, Menard D, Lambert M, Bitton A, Sanchez R, et al. Association between genetic variants in the HNF4A gene and childhood-onset Crohn's disease. *Genes Immun.* 2012;13:556-65.

37. Wilson A, Reyes E and Ofman J. Prevalence and outcomes of anemia in inflammatory bowel disease: a systematic review of the literature. *Am J Med.* 2004;116 Suppl 7A:44S-49S.

38. Gentschew L, Bishop KS, Han DY, Morgan AR, Fraser AG, Lam WJ, Karunasinghe N, Campbell B and Ferguson LR. Selenium, selenoprotein genes and Crohn's disease in a case-control population from Auckland, New Zealand. *Nutrients.* 2012;4:1247-59.

39. Lauc G, Huffman JE, Pucic M, Zgaga L, Adamczyk B, Muzinic A, Novokmet M, Polasek O, Gornik O, Kristic J, et al. Loci associated with N-glycosylation of human immunoglobulin G show pleiotropy with autoimmune diseases and haematological cancers. *PLoS genetics.* 2013;9:e1003225.

40. Plomp R, Ruhaak LR, Uh HW, Reiding KR, Selman M, Houwing-Duistermaat JJ, Slagboom PE, Beekman M and Wuhrer M. Subclass-specific IgG glycosylation is associated with markers of inflammation and metabolic health. *Sci Rep.* 2017;7:12325.

41. Li T, DiLillo DJ, Bournazos S, Giddens JP, Ravetch JV and Wang LX. Modulating IgG effector function by Fc glycan engineering. *Proc Natl Acad Sci U S A.* 2017;114:3485-3490.

Table 1. Characteristics of the pharmacogenomics study participants

Characteristics	Colchicine (N=767)	Placebo (N=755)
Female sex, N (%)	145 (18.9%)	139 (18.4%)
Age, mean \pm SD, Year	60.7 \pm 10.0	60.8 \pm 9.9
BMI *, mean \pm SD, kg/m ²	28.7 \pm 4.9	29.1 \pm 4.5
Current smoker, N (%)	180 (23.5%)	164 (21.7%)
Diabetes, N (%)	123 (16.0%)	129 (17.1%)
Hypertension, N (%)	368 (48.0%)	363 (48.1%)
Dyslipidemia, N (%)	393 (51.2%)	366 (48.5%)
Prior MI, N (%)	114 (14.9%)	113 (15.0%)
Prior PCI, N (%)	141 (18.4%)	136 (18.0%)
Prior CABG, N (%)	29 (3.8%)	33 (4.4%)
Prior stroke, N (%)	19 (2.5%)	22 (2.9%)
Prior heart failure, N (%)	8 (1.0%)	10 (1.3%)
History of atrial fibrillation, N (%)	39 (5.1%)	34 (4.5%)
<i>Concomitant medication</i>		
Aspirin, N (%)	762 (99.3%)	749 (99.2%)
Anti-platelet agent other than aspirin *, N (%)	755 (98.4%)	751 (99.5%)
Statin, N (%)	762 (99.3%)	751 (99.5%)
Beta-blocker, N (%)	683 (89.0%)	664 (87.9%)

* Significantly different between treatment groups, all variables tested by Kruskal-Wallis or Chi-Squared test. BMI: body mass index; CABG: coronary artery bypass graft; MI: myocardial infarction; N: number of patients; PCI: percutaneous coronary intervention.

Table 2. Genetic association results of the leading genetic variants found to be significantly associated in the COLCOT pharmacogenomic study

Endpoint	Leading variant	EA	EAF	COLCOT arm	N total	N Events (%)	HR (95% CI)	P value	Int. P value*
Gastrointestinal adverse events	rs6916345 chr6:14649353	A	0.50	Colchicine	751	183 (24.4)	1.89 (1.52-2.35)	7.41×10 ⁻⁹	2.96×10 ⁻⁸
				Placebo	741	168 (22.7)	1.30 (1.04-1.62)	0.02	
	rs74795203 chr10:13377992	G	0.06	Colchicine	764	187 (24.5)	2.51 (1.82-3.47)	2.70×10 ⁻⁸	3.13×10 ⁻⁶
				Placebo	751	173 (23.0)	0.71 (0.46-1.09)	0.11	

Chr: chromosome; EA: effect allele; EAF: effect allele frequency in COLCOT population; HR: hazard ratio; Int.: interaction; N: number of patients. Reported results are for Cox proportional hazards regression adjusted for age, sex, and 10 principal components for genetic ancestry. * Interaction P value represents the association result for the variant by colchicine interaction term. Chromosomal position reporting according to GRCh37.



Table 3. Effect of colchicine on gastrointestinal adverse events compared to placebo stratified by genotype groups

Endpoint	Leading Variant	Genotype	Group %	N Total	N with Events	% Events Colchicine	% Events Placebo	HR (95% CI)	P-value*
Gastrointestinal adverse events	rs6916345 chr6:14649353	GG	25%	383	80	13.7%	28.0%	0.43 (0.26-0.69)	5.45×10 ⁻⁴
		AG	50%	742	167	23.2%	21.8%	1.08 (0.80-1.47)	0.61
		AA	25%	367	104	36.9%	18.6%	2.42 (1.57-3.72)	5.77×10 ⁻⁵
	rs74795203 chr10:13377992	AA	87%	1319	299	21.6%	23.8%	0.88 (0.70-1.11)	0.28
		AG	12%	186	59	47.6%	19.2%	3.79 (2.13-6.73)	5.57×10 ⁻⁶
		GG	1%	10	2	-	-	-	-
		AG+GG	13%	196	61	47.1%	18.9%	3.98 (2.24-7.07)	2.33 ×10 ⁻⁶

Chr: chromosome; CI: confidence interval; HR: hazard ratio; N: number of patients. * P value is comparing colchicine versus placebo by Cox proportional hazards regression adjusted for age, sex, and 10 principal components for genetic ancestry. Chromosomal position reporting according to GRCh37.

Figure Legends:

Figure 1. Manhattan plot for the GWAS of gastrointestinal adverse events in COLCOT using Cox proportional hazards regression with 4,468,817 genetic variants of minor allele frequency \geq 5% with 767 patients from the colchicine arm of COLCOT, controlling for age, sex, and principal components for genetic ancestry.



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