American Heart Association.

GPM Journal Bytes

A quarterly online publication of journal summaries brought to you by the American Heart Association's **Council on Genomic and Precision Medicine**.

The opinions of the summary authors in this publication are their own and not necessarily those of the American Heart Association.

Dear Colleagues,

This issue of Journal Bytes highlights several cutting edge and fascinating studies from 2021. As you know, GPM Journal Bytes is intended to summarize important and relevant papers from multiple journal sources in the realm of genomic and precision medicine from the past quarter and provide concise summaries

Our desire is to help save you time and keep you well informed. We welcome any suggestions you may have to help us make Journal Bytes serve you better. If you have any suggestions, or questions, please do not hesitate to contact us. And please do not forget to follow the GPM Council on twitter @GenPrecisionMed.

Best wishes,
Sharon Cresci MD, FAHA, FACC, FASE
Chair, GPM Professional/Public Education & Publications Committee

Is a "Once-and-Done" Treatment for Atherosclerotic Cardiovascular Disease on the Horizon?

Anjali Tiku Owens, MD
@tikuowens
University of Pennsylvania Perelman School of Medicine

Musunuru, K., Chadwick, A.C., Mizoguchi, T. *et al.* In vivo CRISPR base editing of *PCSK9* durably lowers cholesterol in primates. *Nature* 593, 429–434 (2021).

Naturally occurring loss-of-function variants in *PCSK9* result in lower levels of LDL cholesterol and a reduced risk of developing atherosclerotic cardiovascular disease, which remains the leading cause of death globally. PCSK9 is preferentially expressed in the liver and is a potential target for in vivo gene editing using CRISPR technology. In this paper, the authors report the first proof-of-concept study in monkeys of CRISPR base editors delivered in vivo to make precise single nucleotide changes in *PCSK9* in the liver. A single infusion of lipid nanoparticles resulted in a reduction of blood levels of PCSK9 of ~ 90% and reduction of LDL cholesterol of ~ 60% with sustained response over at least 8 months. In vivo gene editing is a promising approach to target candidate genes in the liver via a lipid nanoparticle delivery system.

American Heart Association.

GPM Journal Bytes

A quarterly online publication of journal summaries brought to you by the American Heart Association's **Council on Genomic and Precision Medicine**.

A Step Toward Explaining Variable Expression in Hypertrophic Cardiomyopathy

Sharon Cresci, MD, FAHA, FACC, FASE
@SharonCresciMD
Washington University School of Medicine

Tadros R, Francis C, Xu X, Vermeer AMC, Harper AR, Huurman R, et al. Shared genetic pathways contribute to risk of hypertrophic and dilated cardiomyopathies with opposite directions of effect. *Nat Genet*. 2021 Feb:128-134. PMID: 33495596; PMCID: PMC7611259

Historically, variable expression in patients with Hypertrophic Cardiomyopathy (HCM) has been attributed to a complex interplay of genetic, environmental, and molecular factors but specific modulators have not been well delineated. Tadros et al performed a meta-analysis of GWAS that included a total of 1,733 unrelated HCM cases (37% with an identified pathogenic or likely pathogenic variant) and 6,628 controls; 5,521 dilated cardiomyopathy (DCM) cases and 397,323 controls; and 19,260 UK biobank participants with structurally normal hearts in whom they defined 9 left ventricular (LV) traits by MRI. They identified 16 variants associated with HCM, 13 with DCM, and 23 with LV traits, and found that 8 of the 16 variants associated with HCM were also associated with DCM but with opposite direction of effect. The authors further assessed whether common variants could explain variability in HCM expression and found that a weighted polygenic risk score comprised of 20 common variants could explain a significant portion of variability in HCM expression (h^2_{SNP} estimates ranging from 0.12 to 0.29). These findings demonstrate that background genetic variation contributes to the variable expression observed in patients with HCM and provide important insights into genetic pathways that are responsible for both HCM and DCM but with opposite direction of effects.

A Deep Dive into the Biology of Platelet Reactivity

Sony Tuteja, PharmD, MS
@sony_tuteja
University of Pennsylvania Perelman School of Medicine

Keramati AR, Chen MH, Rodrigues BAT, Yanek LR, Bhan A, Gaynor BJ, et al. Genome sequencing unveils a regulatory landscape of platelet reactivity. *Nature Communications* 2021; Jun 15; 12 (1): 3626. PMID: 34131117

American Heart Association.

GPM Journal Bytes

A quarterly online publication of journal summaries brought to you by the American Heart Association's **Council on Genomic and Precision Medicine**.

Platelet aggregation at the site of vascular wall injury is central to the pathogenesis of ASCVD. A whole-genome sequencing (WGS) analysis was performed in 3,855 participants of the NHLBI Trans-Omics for Precision Medicine (TOPMed) program for phenotypes related to platelet aggregation in response to agonist stimulation to determine the contribution of both common and rare variants. 14 novel and 2 known independent significant loci were identified and replicated in another dataset; of these, the lead variants in PEAR1 and RGS18 were eQTLs for *PEAR1* and *RGS18*. PheWAS analysis in external biobanks showed the minor allele of *PEAR1* (rs12041331) to be associated with and increased odds of gastrointestinal bleeding and *RGS18* (rs1175170) associated with arterial thrombosis/embolization. Rare variant analysis showed significant findings for *SVEP1* and ADP-induced platelet aggregation through a nonsynonymous variant Gly229Arg (MAF 0.028). This study provides further insight into the genetic determinants of platelet function traits which may aid in the early prediction of thrombosis and tailoring of antiplatelet therapies.

Mavacamten and Quality of Life in Hypertrophic Cardiomyopathy

Ferhaan Ahmad, MD, PhD, FAHA, FACC
@FerhaanAhmad
University of Iowa Carver College of Medicine

Spertus JA, Fine JT, Elliott P, Ho CY, Olivotto I, Saberi S, Li W, Dolan C, Reaney M, Sehnert AJ, Jacoby D. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): health status analysis of a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2021 Jun 26;397(10293):2467-2475. doi: 10.1016/S0140-6736(21)00763-7. Epub 2021 May 15. PMID: 34004177.

Mavacamten is a first-in-class cardiac myosin inhibitor that was recently shown in a placebo-controlled, randomized, phase 3 trial (EXPLORER-HCM) to improve peak oxygen consumption on exercise and New Your Heart Association (NYHA) class in patients with obstructive hypertrophic cardiomyopathy (HCM). In this secondary analysis, the Kansas City Cardiomyopathy Questionnaire (KCCQ) was serially administered to determine the effect of mavacamten on symptoms, physical and social function, and quality of life. After 30 weeks of treatment, the improvement in the KCCQ-OS score was greater in subjects randomized to mavacamten compared with placebo (mean score change 14·9 [SD 15·8] vs 5·4 [13·7], $p<0·0001$). The magnitude of the improvement in the KCCQ score was similar to that seen in other studies of patients undergoing percutaneous or surgical aortic and mitral valve interventions. Importantly, the beneficial effects of mavacamten were lost within 8 weeks following termination of therapy.

American Heart Association.

GPM Journal Bytes

A quarterly online publication of journal summaries brought to you by the American Heart Association's **Council on Genomic and Precision Medicine**.

A Trial of Precision Medicine Approach in Patients with Cardiovascular Disease and Chronic Kidney Disease

Naveen Pereira MD, FACC, FRCPE, FAHA
@nl_pereira
Mayo Clinic

Paul M Ridker 1, Matt Devalaraja 2, Florian M M Baeres 3, Mads D M Engelmann 3, et al., RESCUE Investigators. IL-6 inhibition with ziltivekimab in patients at high atherosclerotic risk (RESCUE): a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet*. 2021 May 29;397(10289):2060-2069. doi: 10.1016/S0140-6736(21)00520-1. Epub 2021 May 17. PMID: 34015342 DOI: 10.1016/S0140-6736(21)00520-1

The goal of precision medicine is to target the right person with the right drug to enhance effectiveness of therapy and minimize toxicity in the overall disease population. There have been successful examples of using this approach, especially in oncology, and recent trials targeting patients in cardiovascular subgroups with specific therapy have been initiated. In the past, Ridker et al had tested Canakinumab in the CANTOS trial and showed that 150 mg dosage reduced myocardial infarction, stroke and cardiovascular death; however, the drug was associated with a higher incidence of fatal infections. The investigators subsequently showed that those in whom hsCRP levels were reduced to less than 2 mg/L had the most benefit. In this report, Ridker et al report the results of a precision medicine Phase 2 trial in which patients with elevated high-sensitivity CRP and moderate to severe chronic kidney disease who are at high risk for coronary events were randomized to subcutaneous placebo or ziltivekimab at different doses every 4 weeks up to 24 weeks. The authors demonstrate that reduction in hsCRP levels at 12 weeks (the primary outcome of the trial) was 77% to 92% in the ziltivekimab groups and just 4% in the placebo group. These findings form the basis for a phase 3 larger clinical outcomes trial in this patient sub-population with known cardiovascular disease.

Ferhaan Ahmad
@FerhaanAhmad

Sharon Cresci
@SharonCresciMD

Anjali Tiku Owens
@tikuowens

Naveen Pereira
@nl_pereira

Sony Tuteja
@sony_tuteja

The opinions of the summary authors in this publication are their own and not necessarily those of the American Heart Association.