Toward personalized medicine for cardiovascular pharmacotherapy

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This editorial refers to ‘Polygenic risk score for ACE-inhibitor-associated cough based on the discovery of new genetic loci’, by J. Ghouse et al., https://doi.org/10.1093/eurheartj/ehac322.

Graphical Abstract

(A) Role of some of the genetic loci associated with angiotensin-converting enzyme inhibitor discontinuation due to cough. (B) The authors hypothesized that genetic variants could partly share pathophysiological pathways, so that genetic susceptibility to ACEiAC could in part be driven by an innate cough sensitization, which progresses into cough after exposure to a trigger (e.g. ACEi, GERD, or allergens). Abbreviations: ACE, angiotensin-converting enzyme; ACEi, ACE inhibitor; ACEiAC: ACEi-associated cough; GERD, gastro-oesophageal reflux disease; GWAS, genome-wide association study; NTR1, neurotensin receptor 1.

The opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal or of the European Society of Cardiology.

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The renin–angiotensin–aldosterone system (RAAS) plays a critical role in the pathophysiology of cardiovascular diseases (CVDs). Angiotensin-converting enzyme inhibitors (ACEIs) are first-choice drugs in clinical practice for the treatment of patients with CVD [e.g. heart failure (HF) with reduced ejection fraction, arterial hypertension, coronary artery disease, left ventricular hypertrophy, and atherosclerotic vascular diseases], chronic kidney disease (particularly when accompanied by proteinuria), and diabetes (ACEIs reduced all-cause mortality, CV mortality, and major CV events). In these patients, ACEIs slow disease progression, decrease hospitalization, and improve cardiovascular and renal outcomes.1

Although ACEIs are well tolerated, 14–30% of patients discontinue treatment, mainly because of adverse drug reactions (ADRs), the most common ADR being persistent, dry, irritating cough that can start within days to months after therapy initiation; consequently, ACEI withdrawal is required to alleviate the cough.2,3 The incidence of cough ranges from 1.5% to 23% (mean, 10%; median, 9%).2 Notably, ACEI-associated cough (ACEIAC) is not dose dependent and appears to occur only in susceptible individuals, although individual susceptibility is not fully understood.

Cough is an interplay between cough triggers (e.g. ACEI treatment) and cough sensitization of both the peripheral and central neural pathways capable of eliciting cough at lower levels of a given stimulus (i.e. cough hypersensitivity syndrome).3 A major challenge is understanding the heterogeneity underlying the development and persistence of chronic cough in different patients. Although the exact mechanism of ACEI-induced cough remains unclear, several theories have been postulated.

- (i) Accumulation of the protrusive and pro-inflammatory mediators bradykinin and substance P, by ACEI in the respiratory tract, leading to the contraction of airway smooth muscle and thus cough. Bradykinin substance P may sensitize bronchopulmonary vagal afferent fibres, leading to neurogenically mediated cough.4 Bradykinin also activates phospholipase A2, leading to the generation of arachidonic acid derivatives (leukotrienes, histamines, and prostaglandin I2 and E2), which may cause cough, bronchospasm, and nasal discharge.6
- (ii) Enhanced acetylcholine-induced contraction (sensitization) via muscarinic (M3) receptors expressed in bronchial smooth muscles.3 Activation of the M3 signalling [protein Gq/11]–phospholipase C–protein kinase C–inositol 1,4,5-trisphosphate] pathway increases intracellular Ca2+ leading to bronchoconstriction.
- (iii) Gene polymorphisms. Epidemiological data suggest a genetic predisposition for ACEIAC. The incidence of cough is >2.5 times higher in Asians than in Caucasians.5 Candidate gene studies in small trials and five genome-wide association studies (GWAS) analysed the associations among genetic variations in ACE (ACE I/D polymorphism) and bradykinin pathway members [bradykinin B2 receptor (BDKRB2), bradykinin metabolism (XPNPEP2 encoding aminopeptidase P), membrane metallo-endopeptidase/neprilysin (MME), prostaglandin E receptor (PTGER3), and neurokinin 2 receptor (NK2R)] in ACEI-associated ADRs. However, only one GWAS (1595 cases and 3485 controls) identified six single nucleotide polymorphisms (SNPs) in intron 4 of KCNIP4 associated with ACEIAC.8

Healthcare professionals aim to prescribe the most effective and safe drug for a given indication. However, clinicians currently cannot predict who will develop ACEIAC before starting treatment; clinical guidelines recommend that in patients who develop ACEIAC, ACEI treatment should be discontinued, or switched, to angiotensin receptor blockers (ARBs).9 Therefore, better patient–drug matching methods are needed to minimize ACEIAC. Thus, understanding the interindividual differences in the development of ADRs following therapy is essential for personalized treatment. Recent evidence has shown that switching from ACEIs to ARBs is the best marker in prescription databases and might be useful for investigating the genetic and environmental risk factors associated with ACEI-induced occurrence.10 In this issue of the European Heart Journal, Ghouse et al.11 explored whether ADR information can be deduced from prescription patterns. They used prescription data from three population-based cohorts, UK Biobank, the Copenhagen Hospital Biobank, and deCODE genetics in the Icelandic population, to identify individuals who switched from an ACEI to an ARB, serving as a proxy for ADR, and determined whether associated variants were related to ACEIAC occurrence. The authors conducted a large GWAS on ACEI discontinuation, including 33 959 cases (individuals who switched from an ACEI to an ARB) and 44 041 controls, who continued ACEI treatment for ≥1 year and had no history of an ACEI to ARB switch. Continuous treatment was defined as a maximum of 180 days between successive prescription renewals. The authors identified genome-wide loci (KCN2A, KCNIP4, SRBD1, PREP, SCAI, L3M8TL4, and SLCO4A1/NTSR1; six of these were previously unreported) associated with ACEI discontinuation. The strongest association was observed for the KCNIP4 locus as previously mentioned.8 All lead SNPs were located in non-coding regions, and the majority of variants were not associated with common causes of chronic cough, suggesting a specific role for ACEI discontinuation. Five of the seven lead variants were associated with the expression of one or more genes in at least one tissue and with ACEIAC, but none was associated with ACEI-associated angioedema. By incorporating the identified loci into a polygenic risk score (PRS), they found a dose–response relationship between higher scores and the risk of ACEIAC, but no association was found between increasing quintiles of PRS and the risk of ACEI-associated angioedema. However, the authors did not find evidence to support a causal role for ACEI discontinuation with five pre-defined traits: cough on most days, gastrointestinal reflux diseases, allergic diseases (asthma, rhinitis, and hay fever), chronic pain, and systolic blood pressure.

Notably, two of the identified risk loci were located near KCN2A and KCNIP4, which encode potassium voltage-gated ion channel subfamily members 2 (Kv1.2) and 4 (Kv1.4), respectively, which play important roles in determining neuronal firing properties and regulating neuronal excitability.12 Delayed rectifier Kv1.2 channels express A-type K+ currents that play a pre-synaptic role and prevent hyper-excitability and aberrant action potential firing. Rapidly inactivating 4-aminopyridine (4-AP)-sensitive K+ channels are members of the KCNH1 family of EF hand (helix-loop–helix)–containing calcium-binding proteins that may regulate A-type currents and neuronal excitability in response to changes in intracellular calcium. Blockade of KCN2A-encoded Kv1.2 channels with dalfampridine (4-AP) stimulated capsaicin-sensitive sensory neurons and induced airway vagal afferent nerve discharge and cough in animal models.13
Gouse et al. hypothesized that innate susceptibility to cough sensitization due to inborn changes in ion channel activity may represent one of the contributing mechanisms of ACEIAC. PREP encodes prolyl endopeptidase, which is involved in the maturation and degradation of several vasoactive peptides shorter than 30-mer (bradykinin, angiotensin, substance P, vasopressin, and neurotensin). Thus, impaired breakdown of bradykinin via ACE inhibition combined with reduced expression of PREP may increase the risk of cough via the bradykinin pathway.

NTSR1 encodes the G-protein-coupled neurotensin receptor 1. Neuropeptides and their receptors are expressed in brainstem nuclei engaged in respiration control and the lungs. Neurotensin receptors are synthesized and transported within a subpopulation of afferent and efferent vagal fibres and have been identified in pre-synaptic cholinergic terminals and post-synaptic bronchial smooth muscle cells. Contradictory results were reported in isolated guinea-pig and rat tracheal preparations. In a murine model of hapten-induced asthma, neurotensin reduced airway responsiveness to nebulized methacholine and reduced the number of inflammatory cells in the bronchoalveolar lavage fluid and pro-inflammatory cytokine production. Thereby, neurotensin can modulate airway hypersensitivity via airway vagal nerve innervation and inflammation. However, the possible roles of the other three genetic loci, i.e. SRBD1 (encoding the S1 RNA-binding domain 1), SCAT (encoding the suppressor of cancer cell invasion), and L3MBTL4 (encoding the lethal3 malignant brain tumour-like protein 4) in ACEIAC pathophysiology were not discussed. Thus, Gouse et al. showed that genetic variants affecting neuronal excitability, impaired bradykinin metabolism, and/or airway inflammation may explain, at least partly, the interindividual variability observed in ACEIAC. The authors mentioned the main limitations of this study as follows. In particular, to avoid biases due to population stratification, they excluded persons of non-European ancestry, i.e. blacks and Asians. However, the incidence of ACEI-induced angioedema and ACEIAC is up to five times greater in the people of African descent and Asians than in those of Western descent. Therefore, the present results can only be extrapolated to populations of European ancestry but not to other races/ethnicities. Other genetic variants beyond the sentinel SNPs reported in this study may be associated with ACEIAC, particularly in patients with non-European ancestry. Additionally, because of the low SNP-based heritability, even if genotyping becomes the standard of care in healthcare systems, the results of genetic tests should be integrated with other non-genetic risk factors (clinical and socioeconomic) to facilitate more informed drug selection.

In conclusion, this large, well-designed GWAS emphasized the advantages of utilizing prescription data of population-based cohorts to search for individuals who switched from an ACEI to an ARB or to sacubitril–valsartan in the case of HF, and to improve our understanding of genetic variants linked to ACEI-associated ADRs leading to drug discontinuation. The authors identified seven lead variants (six were novel) associated with ACEIAC, but not with ACEI-associated angioedema, which can help identify people at risk and provide new insights into the pathophysiological mechanisms underlying ACEIAC and other ACEI-associated ADRs.

Conflict of interest: None declared.

Data availability
No new data were generated or analysed in support of this research.

References