

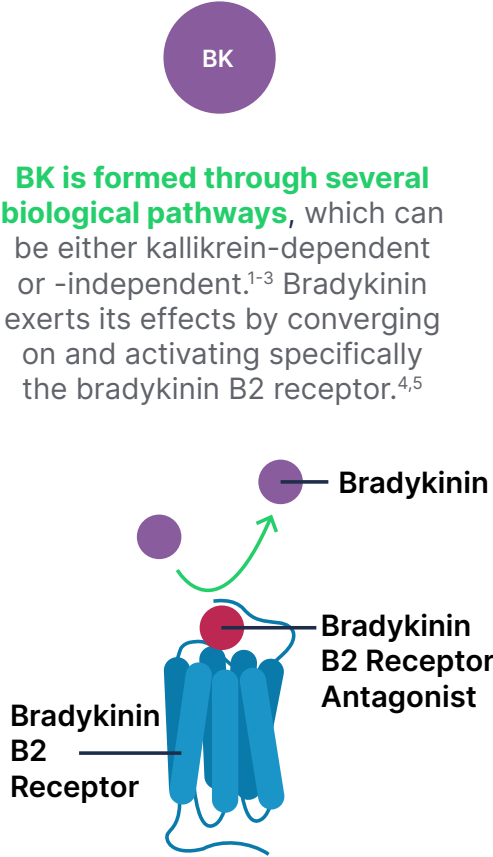


Bradykinin-Mediated Angioedema: Pathways, Physiology, and Disease Mechanism

The publication of this infographic was funded by Pharvaris, and is based on a Pharvaris-sponsored symposium which took place on the 29th May 2025 in Budapest, Hungary.
EMJ. 2025; <https://doi.org/10.33590/emj/KHZH2916>



Bradykinin Production



The dysregulation of bradykinin B2 receptor signalling can contribute significantly to a range of inflammatory disorders^{6,7}

Bradykinin B2 Receptor Antagonism

Consequently, B2 receptor antagonism represents a potential therapeutic target for AE-BK, characterised by vascular leakage and tissue swelling.^{6,7}

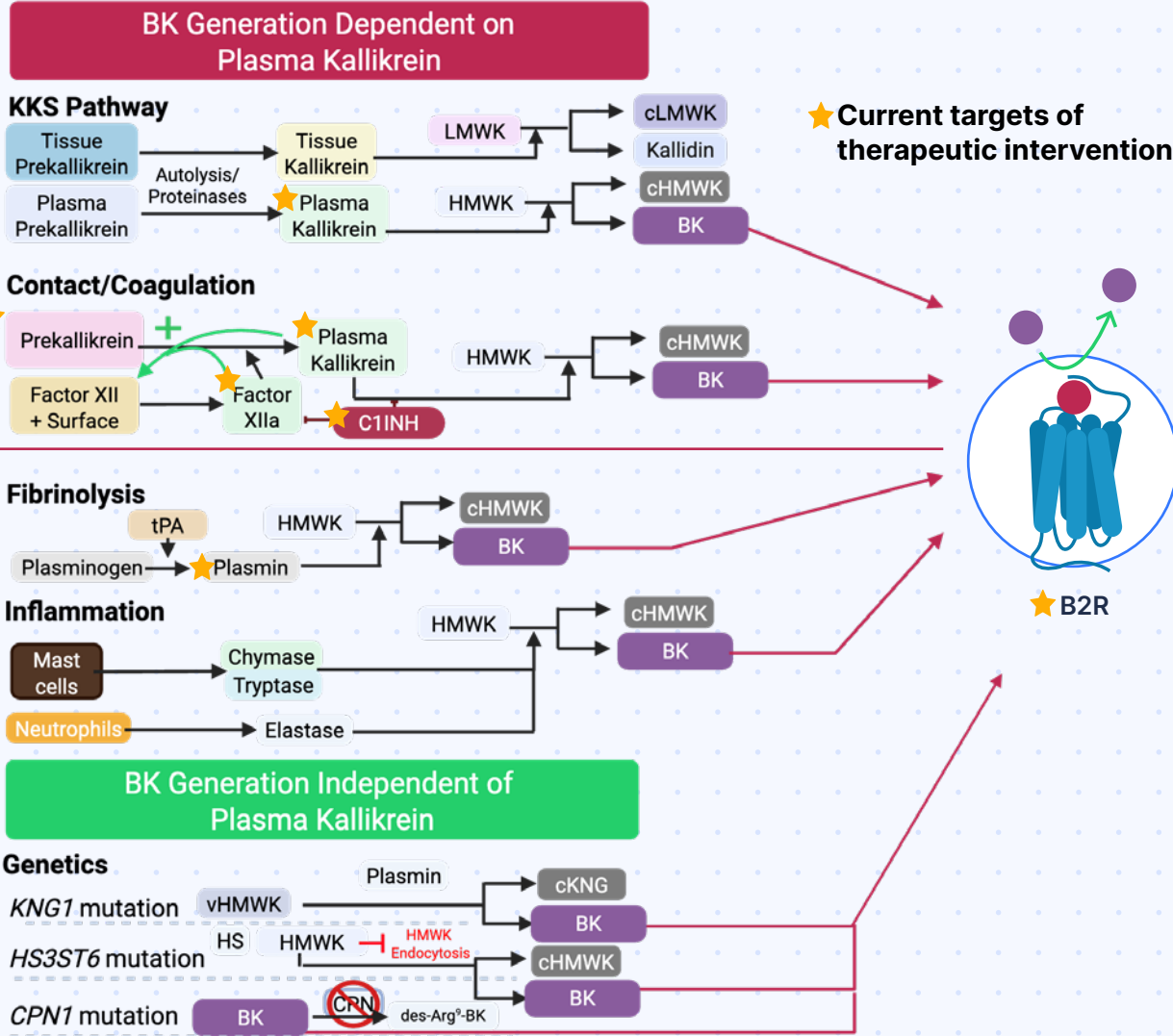
Based on their pathophysiology, bradykinin B2 receptor antagonism has been investigated for potential therapeutic effects in:

HEREDITARY ANGIOEDEMA
Had significant therapeutic effects in the acute treatment setting⁸

CHRONIC SEVERE ASTHMA
Improvement in measured pulmonary function vs placebo; however, there was no significant clinical benefit⁹

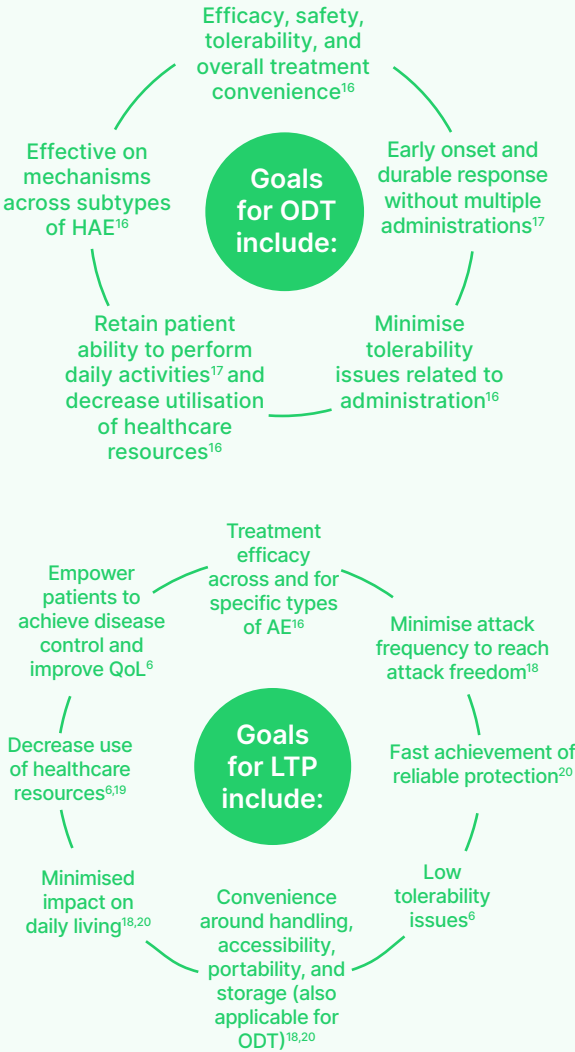
INTRADIALYTIC HYPOTENSION
Reduced the reduction in blood pressure in patients with IDH, and had no evident effects in patients without IDH¹⁰

COLD-INDUCED URTICARIAL SYNDROME
Had effects on cold-induced urticarial symptoms including rash and headache¹¹



Unmet Needs in AE-BK

Unmet needs in AE-BK for ODT and LTP management approaches should address underlying mechanisms from all subgroups of AE-BK, as well as patient needs and expectations.



Characterising AE-BK

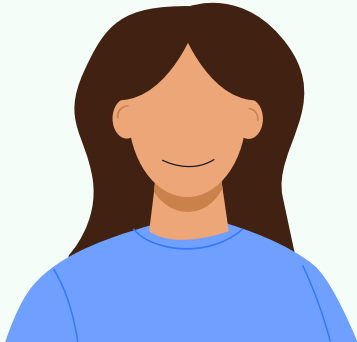
The WAO/EAACI guidelines, and more recently the DANCE consensus, were developed to provide global consensus in defining different subtypes of AE.^{6,12}



The differential diagnosis of AE subtypes remains **complex and time-consuming**, driving ongoing efforts to identify measurable biomarkers to facilitate the **diagnosis and classification** of AE-BK and AE subtypes.¹³



Moreover, access to testing procedures varies between clinics, causing delays in diagnosis.⁶ **Pathway-specific testing is limited**, with current diagnostic indicators unable to distinguish between AE-BK and other AE types.^{14,15}



Abbreviations: AE: angioedema; Arg: arginine; BK: bradykinin; cHMWK: cleaved high molecular weight kininogen; cLMWK: cleaved low molecular weight kininogen; CPN: carboxypeptidase N; CPN1: carboxypeptidase N 1 gene; cKNG: cleaved kininogen; DANCE: Definition, Acronyms, Nomenclature, & Classification of Angioedema; FXII: Factor 12; HAE: hereditary angioedema; HMWK: high molecular weight kininogen; HS: heparan sulfate; HS3ST6: heparan sulfate 3-O-sulfotransferase 6 gene; IDH: intradialytic hypotension; KKS: kallikrein-kinin system; KNG1: kininogen 1 gene; LMWK: low molecular weight kininogen; LTP: long-term prophylactic; ODT: on-demand; QoL: quality-of-life; tPA: tissue plasminogen activator; v: variant; WAO/EAACI: World Allergy Organization/European Academy of Allergy and Clinical Immunology.

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