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Review

Mechanism and Individualized Management of Hypertension Associated With Bruton Tyrosine Kinase Inhibitors: The *PCSK9/Notch3* Signaling Pathway

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Abstract

Bruton's tyrosine kinase inhibitors (BTKIs) have become the first-line treatment for B-cell malignancies such as chronic lymphocytic leukemia, significantly improving patient outcomes. However, hypertension is a common and critical cardiovascular adverse effect of BTKIs, with incidence rates ranging from 23% to 75%. For some patients, traditional antihypertensive therapy is ineffective, creating significant risks to cardiovascular safety and the sustainability of the treatment plan. Current reviews have primarily addressed general BTKI cardiotoxicity or isolated signaling pathways, failing to systematically analyze how the *proprotein convertase subtilisin/kexin type 9 (PCSK9)/Notch3* pathway coordinates hypertension. Furthermore, current reviews lack comprehensive integration of individual susceptibility and mechanism-targeted strategies. Thus, this review systematically evaluates the epidemiological characteristics, molecular mechanisms, individual risk-modifying factors, and management strategies of BTKI-related hypertension by searching the PubMed, Embase, and Web of Science databases (up to 2025). Key findings suggest that BTKIs induce endothelial dysfunction and increase peripheral mechanisms through multiple mechanisms. These agents promote vascular inflammation, remodeling, and altered lipid metabolism by upregulating *PCSK9*, abnormally activating *Notch3* signaling, increasing renin–angiotensin–aldosterone system activity, and driving nicotinamide adenine dinucleotide phosphate (NADPH) oxidase–reactive oxygen species-mediated oxidative stress. Additionally, off-target inhibition of TEC/interleukin 2-inducible T-cell kinase contributes to these adverse vascular effects. Disease risk is further modified by *Notch3/PCSK9* gene polymorphisms and clinical features such as existing cardiovascular disease and advanced age. Clinical management primarily relies on traditional antihypertensive drugs such as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, as well as calcium channel blockers. In contrast, novel intervention strategies such as PCSK9 inhibitors and curcumin show potential advantages. To our knowledge, this review systematically elaborates the core role of the *PCSK9/Notch3* signaling pathway in BTKI-related hypertension, integrating the "mechanism – susceptibility – intervention" three-dimensional network, providing a theoretical basis for precise risk stratification and individualized treatment, and promoting the dual optimization of cardiovascular protection and anti-tumor therapy.

Keywords: Bruton's tyrosine kinase inhibitor; hypertension; proprotein convertase subtilisin/kexin type 9; Notch3; signaling pathway; individualized management

1. Introduction

In recent years, Bruton's tyrosine kinase inhibitors (BTKIs) have been established as the first-line standard treatment for B-cell malignancies, especially chronic lymphocytic leukemia (CLL), due to their high efficacy, significantly improving patient outcomes [1]. However, as BTKIs have gained widespread clinical application, their associated cardiovascular toxicity has become increasingly prominent. Specifically, hypertension has emerged as a common, critical adverse reaction with an incidence rate of 23% to 75% [2,3], which is significantly higher than that of the general population and is closely related to an increased risk of major adverse cardiovascular events such as myocardial infarction and heart failure [3]. More importantly, some patients have an inadequate response to conventional antihypertensive drugs [3], suggesting the existence of a unique pathophysiological mechanism distinct from primary hypertension, which urgently requires in-depth exploration.

Current reviews on the cardiotoxicity of BTKI have mainly focused on general adverse events such as atrial fibrillation and myocardial injury, or the influence of specific signaling pathways such as phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) and Toll-like receptor (TLR)/nuclear factor kappa B (NF-κB) [4,5,6]. While studies have addressed the independent roles of proprotein convertase subtilisin/kexin type 9 (PCSK9) and Notch3, substantial knowledge gaps regarding their interaction or combined roles persist. First, the functional axis involving *PCSK9* and *Notch3*, and how they collaboratively mediate

BTKI-related hypertension, remains systematically unclarified. Furthermore, a comprehensive analysis of the molecular interaction mechanism (e.g., signal cross-talk, upstream regulatory relationships) between the two is lacking. Second, the precise interaction between patient-specific factors—including genetic variants (*Notch3, PCSK9*) and clinical characteristics such as cardiovascular disease or advanced age—and the *PCSK9/Notch3* axis remains unclear, which hampers effective risk stratification. Third, the prospective application of interventions targeting this signaling axis (e.g., PCSK9 inhibitors, multi-target regulation by natural compounds) has not been systematically summarized within the context of BTKI-associated hypertension. Due to these knowledge gaps, the mechanism of BTKI-related hypertension remains poorly understood, hindering the development of targeted, individualized management strategies.

Addressing previous gaps, this review uniquely focuses on the *PCSK9/Notch3* signaling axis as the primary driver of BTKI-induced hypertension. We systematically detail the pathological progression—from lipid metabolism disorders and vascular inflammation to remodeling—while integrating individual risk factors such as genetic polymorphisms. By mapping the interplay among BTKI exposure, signaling activation, and patient susceptibility, we provide a comprehensive evaluation of both traditional antihypertensive regimens and novel targeted interventions such as PCSK9 inhibitors and curcumin. Based on a comprehensive search of the PubMed, Embase, and Web of Science databases (up to 2025), this review systematically synthesizes the epidemiology, molecular mechanisms (specifically the *PCSK9/Notch3* axis), and personalized management of BTKI-related hypertension. It fills gaps in current literature by highlighting signaling axes and individualized risk strategies, providing a theoretical basis for precise prevention and treatment to optimize both cardiovascular health and anti-tumor efficacy.

2. Basic Biological Characteristics of *BTK*

2.1 Discovery and Clinical Application of BTK

In 1993, Vetrie et al. [7] utilized positional cloning to isolate a novel gene at the X-linked agammaglobulinemia (XLA) locus. They confirmed that this gene encodes a cytoplasmic protein tyrosine kinase, specifically expressed in B cells, which bears characteristic mutations responsible for XLA. This study identified the gene—now known as *BTK*—as a member of the Src-related family of non-receptor tyrosine kinases. This finding initially defined the biological nature of the *BTK* gene, establishing the essential molecular framework for further functional research and the development of targeted therapies [7]. Based on the B cell-specific expression of *BTK*, Uckun et al. [8] proposed in 1995 that *BTK* and related cluster of differentiation 19 (CD19) tyrosine kinases could serve as therapeutic targets for B cell precursor leukemia [8]. The following year, Uckun FM et al. [9] demonstrated in the DT-40 lymphoma B-cell model that *BTK* is crucial for radiation-induced apoptosis, as *BTK*-deficient cells resisted this process, while the reintroduction of wild-type *BTK* restored it.

As the functional mechanism of *BTK* in B cells becomes increasingly clear, its value as a target for the treatment of B-cell malignancies has been fully validated, and the development of BTKIs has entered the clinical translation stage. In 2009, Pharmacyclics initiated the first global Phase I clinical trial of the selective BTKI PCI-32765 (ibrutinib) [10]. Subsequent research by Advani et al. [11] further confirmed that the drug has good safety and preliminary therapeutic efficacy in B-cell malignancies. On this basis, ibrutinib was first approved in November 2013 for the treatment of relapsed/refractory mantle cell lymphoma (MCL), marking the beginning of the clinical application era of BTKIs. Following their development, the BTKIs acalabrutinib and zanubrutinib were approved in October 2017 and November 2019, respectively, expanding the available clinical options for this drug class. Cardiovascular toxicity was identified early in the clinical development of BTKIs. Specifically, a Phase Ib/II trial conducted by O'Brien et al. [12] involving elderly, treatment-naïve patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) reported a 29% incidence of hypertension, with 6% reaching grade 3 severity. Based on an analysis of clinical data, McMullen et al. [13] found that ibrutinib therapy carries an approximately 10-fold higher risk of atrial fibrillation compared to the general population. Furthermore, they proposed a novel mechanism for this side effect, suggesting that ibrutinib may induce atrial fibrillation by inhibiting the PI3K/Akt signaling pathway within the heart (Fig. 1, Ref. [10]).

2.2 Biological Function and Pathological Role of BTK

The B-cell receptor (BCR) signaling pathway is a core molecular pathway that regulates B-cell development, activation, proliferation, differentiation, and survival. Its dysfunction is closely related to various B-cell malignancies and autoimmune diseases [14,15]. The initial step of BCR activation is receptor cross-linking triggered by binding of the antigen to the receptor, which activates the Src family of kinases (such as Lyn and Fyn); these kinases phosphorylate immunoreceptor tyrosine-based activation motifs (ITAMs) in the intracellular segment of the BCR [16,17]. Phosphorylated ITAMs specifically recruit spleen tyrosine kinase (Syk), and activated Syk further phosphorylates B-cell linker protein (BLNK). As a key scaffold protein, BLNK recruits *BTK* and facilitates its phosphorylation and activation [18].

Activated BTK initiates downstream cascades by phosphorylating the core substrate phospholipase C gamma 2 (PLCγ2), which cleaves phosphatidylinositol-4,5-bisphosphate (PIP_2) on the cell membrane, generating inositol triphosphate (IP_3) and diacylglycerol (DAG).

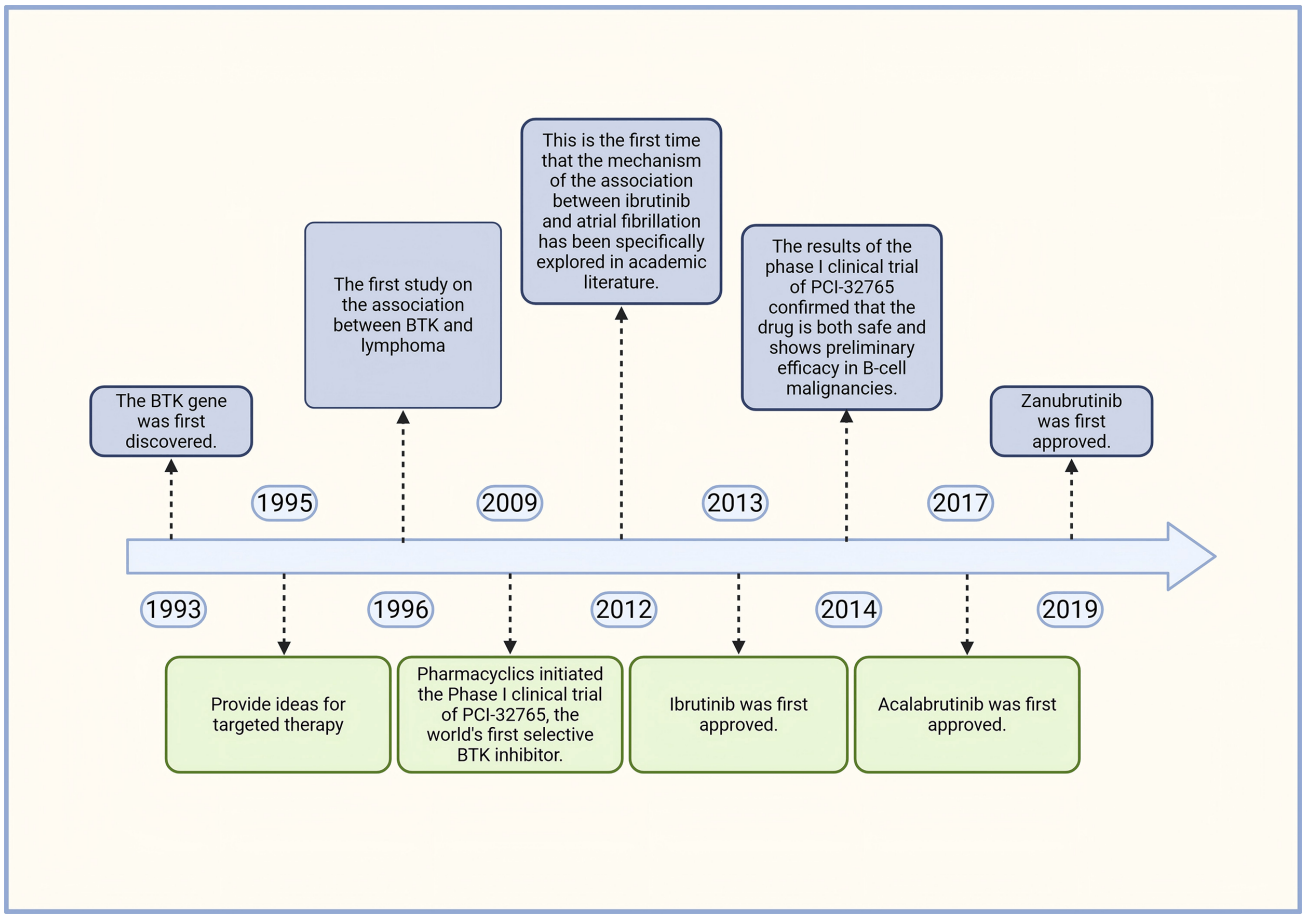

Fig. 1. Milestones of Bruton's tyrosine kinase (*BTK*). This figure summarizes the key time points and significant advancements in the field of *BTK* and Bruton's tyrosine kinase inhibitors (BTKIs). In 1993, the *BTK* gene was first identified (confirming its identity as a Src family tyrosine kinase). In 1995, Provide ideas for targeted therapy.The 1996 study first identified *BTK* as a potential therapeutic target for B-cell malignancies. In 2009, Pharmacyclics initiated the first Phase I clinical trial of the selective BTKI ibrutinib (PCI-32765) globally [10]. In 2012, the academic community first clarified the mechanism by which ibrutinib is associated with atrial fibrillation (mediated through inhibition of the PI3K/Akt pathway). In 2013, ibrutinib was first approved. In 2014, the results of a Phase I clinical study confirmed its safety and preliminary efficacy in B-cell malignancies. In 2017, acalabrutinib was first approved. In 2019, zanubrutinib was first approved. (Chart source: BioRender.com; Date of creation: January 31, 2026).

IP3 mediates calcium influx, and DAG activates protein kinase C beta [19,20], ultimately synergistically activating the three core downstream pathways of NF-κB, mitogen-activated protein kinase (MAPK), and PI3K/Akt [19,20].

The above-mentioned pathways orchestrate the complex physiological modulation of B cells. Specifically, the NF-κB and MAPK pathways collaborate to promote cyclin expression, which transitions the cell cycle from the G1 to S phase during proliferation [21,22]. *BTK* acts as a critical regulator of germinal center stability by sensing the intensity of BCR signals. This molecular sensing directs cell rate: moderate signals drive B cells toward a memory phenotype, whereas strong signals trigger terminal differentiation into plasma cells [23,24]. At the survival level, the PI3K/Akt pathway ensures B-cell survival by inhibiting pro-apoptotic proteins (e.g., B-cell lymphoma 2 [BCL-2]-associated death promoter) and upregulating anti-apoptotic proteins (e.g., BCL-2) [25].

Aberrant activation of the BCR signaling pathway is widely observed in BCLs such as CLL, MCL, and Waldenström macroglobulinemia [14]. As a core kinase in this pathway, *BTK* is persistently activated in various aggressive and indolent BCLs, with activation patterns including antigen-dependent activation (e.g., activated B cell-type diffuse large BCL [DLBCL]), chronic active signaling (e.g., MCL), or antigen-independent "tonic" signaling (e.g., germinal center B-cell-like-type DLBCL), ultimately promoting tumor cell survival, proliferation, and drug resistance through pathways such as NF-κB and PI3K/Akt [14]. Given the pivotal role of *BTK*, BTKIs have become a core therapeutic strategy for B-cell malignancies [26].

3. Epidemiological Characteristics of BTKI-Related Hypertension

Hypertension is a major risk factor for cardiovascular disease, renal failure, stroke, and cognitive decline [27]. Advancements in targeted cancer therapies, combined with an aging population, have significantly extended survival times for patients with cancer. However, treatment-related hypertension—a common adverse event—poses a dual challenge: it can disrupt essential anti-tumor treatments and increase the risk of cardiovascular events [28].

3.1 Differences in the Incidence of Hypertension Among Different BTKIs

Ibrutinib, a first-generation BTKI, exerts its anti-tumor effect by irreversibly binding to the cysteine 481 site of the BTK protein [29,30,31]; however, its clinical use is limited by a 41% discontinuation rate due to adverse, often off-target, effects. Discontinuation is driven by toxicity, with rates of 63.1% in newly diagnosed and 50.2% in patients with relapsed/refractory CLL/SLL [32]. Furthermore, ibrutinib-related hypertension is a significant concern, with early clinical trials indicating that about 23% of patients with CLL develop new or worsened hypertension [2]. Studies on ibrutinib treatment in patients with lymphoma revealed that more than 75% developed new or exacerbated hypertension, which correlated with an increased risk of major cardiovascular events [3].

The incidence of hypertension with second- and third-generation BTKIs is relatively low. Based on ELEVATE-RR Phase III trial data, acalabrutinib was associated with a 9% incidence of hypertension in patients with previously treated CLL [33]. By contrast, in patients with MCL receiving an acalabrutinib combination regimen, the incidence of hypertension was higher, at 16.7% for treatment-naïve patients and 10% for those with relapsed/refractory disease [34]. In studies investigating BTKIs, hypertension and cardiovascular adverse events varied among agents. Phase II data for zanubrutinib in MCL showed a 16.3% incidence of all-grade hypertension, with 4.7% being grade 3 or higher [35]. While the ALPINE trial indicated similar hypertension rates for zanubrutinib and ibrutinib (27.2% vs. 25.3%), the zanubrutinib group demonstrated a lower incidence of cardiac events, such as atrial fibrillation/flutter [36]. In the Phase II study of orelabrutinib for relapsed/refractory CLL/SLL, the incidence of hypertension was 5.0% (1.3% was grade 3) [37]. In comparison, the incidence of grade 3 or higher hypertension with the third-generation BTKI pirtobrutinib was 7.5% [38] (Fig. 2).

3.2 Therapeutic Challenges of BTKI-Related Hypertension

Real-world data indicate that treatment intolerance is the primary reason for ibrutinib discontinuation, accounting for approximately 50% of cases, with hypertension identified as a major adverse event [32,39]. A study evaluating the efficacy of standard antihypertensive treatment for ibrutinib-related hypertension showed that 37.2% of patients required new or increased antihypertensive drug treatment, with most needing the maximum dose recommended by the guidelines to achieve the target blood pressure. Notably, 18% of patients required a combination of at least three antihypertensive drugs, and another 18% failed to reach target blood pressure despite using at least two [3], suggesting that traditional antihypertensive regimens have limited efficacy in this patient group. Currently, the pathogenesis of new-onset or worsening hypertension after ibrutinib treatment is not fully understood [40]; therefore, in-depth investigation of its pathogenesis is crucial for optimizing treatment regimens.

4. Exploration of the Molecular Mechanism of BTKI-Induced Hypertension

The core mechanism by which BTKI induces hypertension involves the coordinated action of multiple signaling pathways: the off-target effect of BTKI inhibits the vascular endothelial growth factor receptor 2 (VEGFR2)-PI3K/Akt pathway, leading to the reduced activity of endothelial nitric oxide synthase (eNOS), decreased NO production, weakened vascular dilation, and increased peripheral resistance [41,42,43]. NADPH oxidase (NOX) generates reactive oxygen species (ROS), exacerbating endothelial oxidative damage [44]. BTKIs may induce related gene mutations, promoting the release of pro-inflammatory factors, activating the NF-κB pathway, and triggering vascular inflammation and smooth muscle proliferation [45,46]. Excessive ROS consumes NO, exacerbating endothelial dysfunction through oxidative stress [47]. Recent studies have shown that BTKIs can upregulate *PCSK9* levels, promoting low-density lipoprotein (LDL) receptor (LDL-R) degradation and endothelial inflammation, while abnormally activating *Notch3* signaling, causing increased vascular smooth muscle contraction and proliferation. Together, these mechanisms drive vascular remodeling and heightened vascular resistance, resulting in elevated blood pressure [48,49].

4.1 Core Role of the PCSK9/Notch3 Signaling Pathway

4.1.1 Physiological Functions of PCSK9

PCSK9 is a serine protease predominantly synthesized and secreted by the liver [50], with lower levels of expression found in the small intestine, pancreas, kidneys, lungs, and central nervous system [51,52]. Initially known as neuroapoptosis regulatory convertase-1, its core physiological function is closely related to the regulation of cholesterol metabolism [51]. *PCSK9* acts as a metabolic regulator by binding to the hepatic LDL-R and steering it toward lysosomal degradation rather than recycling. By depleting available cell-surface receptors, *PCSK9* inhibits the liver's ability to clear LDL cholesterol (LDL-C) from the blood, serving as a primary driver for atherosclerotic cardiovascular disease [53,54].

Generic name of the drug	Mechanism of action	Current indications	The incidence of hypertension in relevant clinical trials
Ibrutinib	irreversibly inhibits BTK at C481 via covalent bond.	1. For the treatment of mantle cell lymphoma (MCL) in patients who have received at least one prior therapy. 2. For the treatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). 3. As a single agent for the first-line treatment of Waldenström macroglobulinemia (WM) in patients who have received at least one prior therapy or are not suitable for chemoimmunotherapy. 4. In combination with rituximab for the treatment of WM.	Patients with chronic lymphocytic leukemia (CLL): In early clinical trials, approximately 23% of patients developed new-onset or worsening hypertension. In a phase Ib/II trial in elderly treatment-naive CLL patients, the incidence was 29% (with 6% being grade 3 hypertension). Patients with lymphoma: Studies have reported that over 75% of patients developed new-onset or worsening hypertension.
Acalabrutinib	irreversibly inhibits BTK at C481 via covalent bond.	1. Adult patients with chronic lymphocytic leukemia (CLL) / small lymphocytic lymphoma (SLL) who have received at least one prior treatment. 2. Adult patients with mantle cell lymphoma (MCL) who have received at least one prior treatment.	In patients with relapsed/refractory chronic lymphocytic leukemia (CLL) (ELEVATE-RR Phase III trial), the incidence of hypertension was 9%. In patients with mantle cell lymphoma (MCL): For treatment-naive patients receiving the combination regimen, the incidence was 16.7%. For relapsed/refractory patients, the incidence was 10.0%.
Zanubrutinib	irreversibly inhibits BTK at C481 via covalent bond.	1. Adult patients with mantle cell lymphoma (MCL) who have received at least one prior treatment. 2. Adult patients with chronic lymphocytic leukemia (CLL) / small lymphocytic lymphoma (SLL). 3. Adult patients with Waldenström macroglobulinemia (WM).	In patients with mantle cell lymphoma (MCL) (Phase II trial), the incidence of hypertension of any grade was 16.3%, and that of grade 3 or above was 4.7%. In patients with relapsed/refractory chronic lymphocytic leukemia (CLL) (ALPINE Phase III trial), the incidence of hypertension was 27.2%, similar to that of the ibrutinib group (25.3%), but the risk of other cardiac events was lower.
Orelabrutinib	irreversibly inhibits BTK at C481 via covalent bond.	1. Adult patients with mantle cell lymphoma (MCL) who have received at least one prior treatment. 2. Adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) who have received at least one prior treatment. 3. Adult patients with marginal zone lymphoma (MZL) who have received at least one prior treatment.	In patients with relapsed/refractory CLL/SLL (Phase II study), the incidence of hypertension was 5.0%, with 1.3% being grade 3.
Pirtobrutinib	Reversible inhibitors of BTK via non-covalent bond formation	1.Adult patients with relapsed or refractory mantle cell lymphoma (MCL) who have received at least two systemic treatments (including Bruton's tyrosine kinase [BTK] inhibitors) in the past.	The incidence rate of grade 3 or higher hypertension in patients with B-cell malignancies (Phase I/II trials) was 7.5%.

Fig. 2. Mechanism of action, approved indications, and incidence of hypertension of commonly used BTKIs. This table summarizes the core features of five clinically used BTKIs and clarifies the mechanism of action of each (ibrutinib, acalabrutinib, zanubrutinib, and orelabrutinib irreversibly inhibit the C481 site of BTK through covalent bonds; pirtobrutinib is a reversible non-covalent BTKI). It lists the current approved indications of each drug, mainly B-cell malignancies such as MCL and chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), and presents the incidence of hypertension in the corresponding clinical trial populations for each drug, highlighting the differences in incidence rates among different drugs and patient groups. (Chart source: BioRender.com; Date of creation: January 31, 2026).

PCSK9 contributes to the pathophysiology of hypertension through multiple mechanisms. Primarily, it activates the TLR4/NF-κB signaling pathway, which induces monocytes and macrophages to release pro-inflammatory factors such as interleukin 1 beta (IL-1β), IL-6, and tumor necrosis factor alpha (TNF-α). This triggers chronic inflammation that damages vascular endothelial function, reduces NO bioavailability, and promotes vasoconstriction, ultimately increasing blood pressure [55,56]. *In-vitro* findings indicate that *PCSK9* may modulate epithelial sodium

channels and promote renal sodium reabsorption, yet this observation is not supported by *in-vivo* animal experiments [57]. Furthermore, ibrutinib contributes to metabolic dysfunction by inhibiting the BCR signaling pathway, which reduces lipoprotein lipase expression and leads to dyslipidemia and free fatty acid imbalance [58]. This process may synergize with PCSK9-mediated cholesterol metabolism disorders to further increase the risk of hypertension.

4.1.2 Physiological Functions of Notch3

The Notch signaling pathway is composed of four receptors and five ligands [59,60]. Among them, the Notch1 signaling pathway mainly functions by antagonizing VEGF signaling [61], whereas *Notch3*, a key member, plays a core role in vascular development and homeostasis regulation [62]. It mediates signal transduction through direct cell-to-cell contact and participates in vascular morphogenesis and functional regulation [63].

Under physiological conditions, *Notch3* binds to the Jagged1 ligand on endothelial cells. This binding triggers a complex involving the Notch intracellular domain and the recombination signal binding protein Jκ, subsequently driving the expression of hairy and enhancer of split *(HES)/HES-related* with YRPW motif (*HEY*) transcription factors [64]. This directly promotes the expression of vascular smooth muscle cell (VSMC) contractile phenotype markers such as alpha-smooth muscle actin, smooth muscle protein 22-alpha, and calmodulin, maintaining the contractile function of VSMCs and the structural stability of the vascular wall [65]. *Notch3* knockout mouse models demonstrate that this receptor is essential for maintaining the contractile phenotype of VSMCs. Specifically, the absence of *Notch3* results in thinner small artery walls, reduced expression of contractile markers (such as smoothelin and smooth muscle myosin heavy chain), and structural changes that make arteries resemble veins [65].

Under pathological conditions, hypoxia or inflammatory stimulation can lead to abnormal activation of *Notch3* signaling: on the one hand, *Notch3* inhibits the pro-contractile transcription factor *Krüppel-like factor 4* (*KLF4*) and upregulates the pro-proliferative transcription factor *KLF5*, driving VSMCs to transform from a contractile phenotype to a synthetic phenotype [66,67]; on the other hand, the proliferation, migration, and anti-apoptotic abilities of synthetic VSMCs are enhanced, and by activating the mammalian target of rapamycin complex 1 (mTORC1) signaling pathway, the pro-proliferative effect mediated by *Notch3* is amplified, ultimately promoting vascular remodeling [68,69]. Preclinical studies have shown that the expression of Notch3 and its downstream effector molecule *HES5* is significantly increased in hypoxic lung tissue and is positively correlated with the pathological process of hypertension [70], suggesting that abnormal activation of the *Notch3* signaling pathway plays a key role in vascular remodeling and blood pressure regulation.

4.1.3 Cooperative Regulatory Mechanism of the PCSK9/Notch3 Signaling Pathway

The regulation of hypertension by the *PCSK9/Notch3* signaling pathway involves multiple aspects of vascular pathophysiology. In endothelial cells, *PCSK9* promotes the ubiquitination and degradation of VEGFR2, inhibits eNOS expression, reduces NO production, causes microvascular sparseness and endothelial dysfunction, and exacerbates vascular tone imbalance [71]. In VSMCs, the high expression of PCSK9 may participate in vascular remodeling by inducing the transformation of VSMCs from a contractile to a synthetic phenotype [72], and the knockout of the *PCSK9* gene can effectively inhibit VSMC proliferation and migration, maintaining the expression of contractile phenotype markers [73].

The *Notch3* signaling pathway has a pro-fibrotic effect on vascular remodeling: abnormal activation of *Notch3* promotes VSMC proliferation and extracellular matrix deposition, leading to vascular wall thickening and fibrosis, and increasing vascular stiffness [74,75]; whereas inhibition of *Notch3* signaling can significantly alleviate pulmonary vascular remodeling and improve hypertension-related pathological changes [74,75]. Based on experimental evidence, the synergistic effect of *PCSK9* and *Notch3* plays a critical role in pulmonary vascular remodeling. Studies have demonstrated that inhibiting PCSK9 using monoclonal antibodies reduces Notch3 expression and subsequently alleviates the severity of pulmonary vascular remodeling [48]. The underlying mechanism suggests that *PCSK9* promotes pulmonary hypertension by directly regulating *Notch3* expression in VSMCs or indirectly activating the *Notch3* signaling pathway through the induction of chronic inflammation and oxidative stress [55,56,68,69]. Although existing studies have confirmed the key role of the *PCSK9/Notch3* pathway in hypertension [49], the specific mechanisms of molecular interaction (e.g., protein–protein interaction, epigenetic regulation, or signal cross-talk) still need further clarification (Fig. 3).

4.2 Off-Target Inhibition-Related Mechanisms: Role of TEC Kinases and IL-2-Induced T-Cell Kinase

The cardiovascular toxicity of ibrutinib is closely related to its extensive off-target kinase inhibition and disruption of key vascular homeostasis pathways [76,77]. Ibrutinib is not entirely selective for BTK, as it can irreversibly bind to the cysteine residues of multiple kinases, including IL-2-induced T-cell kinase (ITK), TEC kinases (e.g., TEC, BMX/Etk), epidermal growth factor receptor (EGFR/ERBB family members), T-cell X-chromosome kinase, certain Src family kinases (e.g., BLK), and Janus kinase 3 [78,79,80]. Comparative analyses confirmed a significant association between cardiovascular side effects and the inhibition of human epidermal growth factor receptor 2 (HER2), HER4, TEC, *ITK*, and EGFR by BTKIs [81,82].

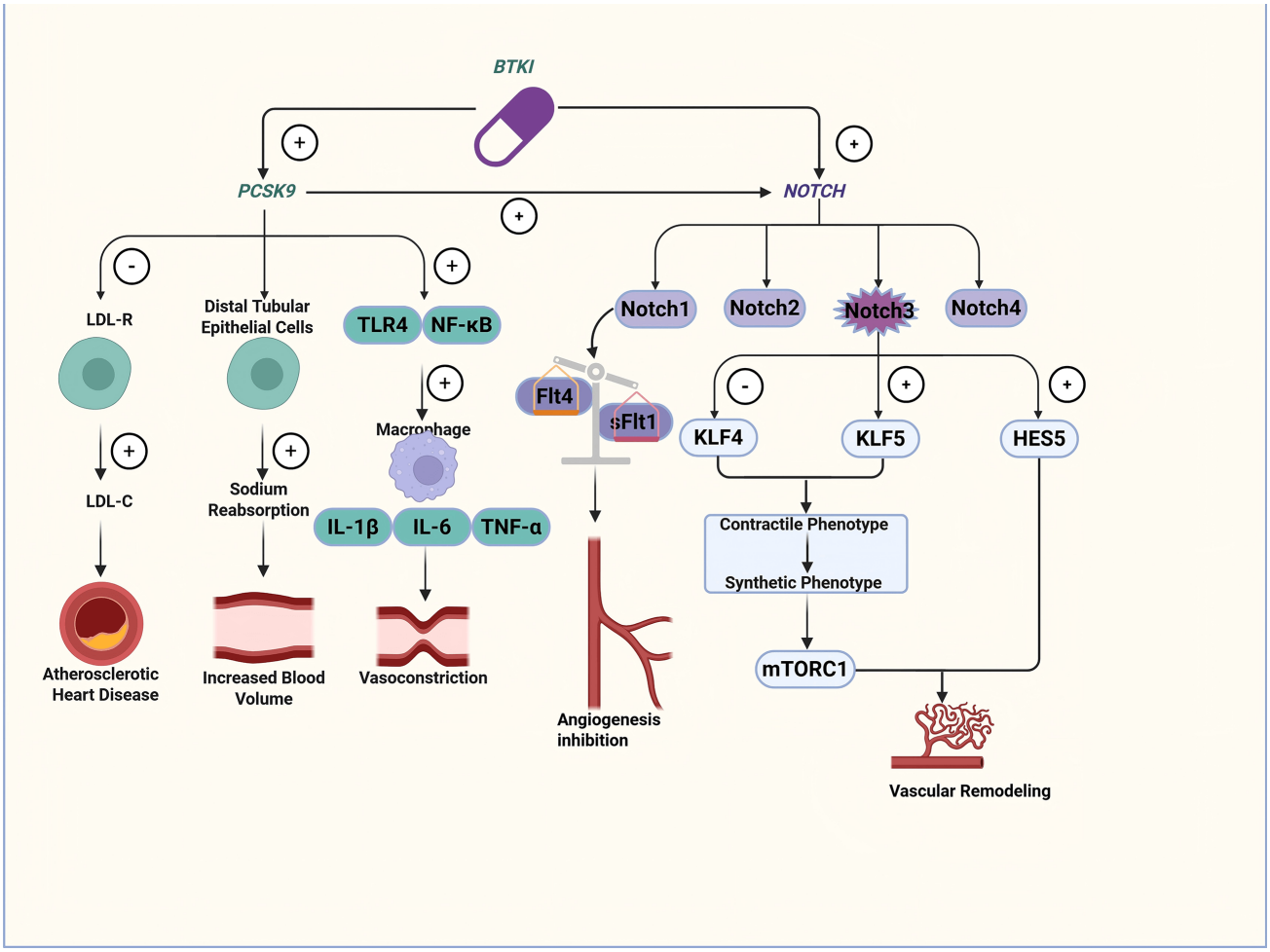

Fig. 3. Proposed mechanism of BTKI involvement in regulating hypertension through the proprotein convertase subtilisin/kexin type 9 (*PCSK9*)/*Notch3* signaling pathway. The mechanism by which BTKIs induce hypertension through the coordinated regulation of the *PCSK9* and *Notch* signaling pathways. On one hand, BTKIs upregulate *PCSK9* expression, thereby inhibiting the function of low-density lipoprotein receptors (LDL-Rs) and leading to an increase in LDL cholesterol (LDL-C) levels. This activates the TLR4/NF-κB inflammatory pathway in distal renal tubular epithelial cells, causing macrophages to release inflammatory factors such as interleukin 1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α), collectively resulting in vasoconstriction and increased sodium reabsorption, thereby promoting the development of hypertension through increased blood volume and the advancement of atherosclerotic heart disease. On the other hand, BTKIs regulate the *Notch* pathway (particularly *Notch3*), driving vascular smooth muscle cells (VSMCs) to transform from a contractile to synthetic phenotype through downstream factors such as *HES5* and *KLF4/5*, and blocking *Notch3-driven* vascular remodeling and angiogenesis through the mammalian target of rapamycin complex 1 (mTORC1) axis, ultimately leading to elevated blood pressure and cardiovascular disease. (Chart source: BioRender.com; Date of creation: October 5, 2025).

4.2.1 Inhibitory Effect by TEC Kinases

Inhibition of TEC kinases is one of the core mechanisms of BTKI cardiovascular toxicity, including hypertension [83]. TEC kinases are a subfamily of non-receptor protein tyrosine kinases expressed in vascular endothelial cells [84], which play multiple key roles in maintaining vascular homeostasis and initiating embryonic vascular formation [85]. BMX/Etk promotes angiogenesis and vasodilation by interacting with and amplifying signals from VEGFRs. It transactivates VEGFR-2 and recruits PI3K [86], while also playing a critical, redundant role downstream of VEGFR and TEK receptor tyrosine kinase signaling [87]. *In vivo* experiments have confirmed that the absence of BMX/Etk inhibits blood flow-mediated angiogenesis and injury repair [88].

Under physiological conditions, TEC kinases play a crucial role as upstream activators of the PI3K/Akt signaling pathway [89]. Once activated, PI3K converts PIP_2 into PIP_3, which acts as a signaling molecule to recruit pyruvate dehydrogenase kinase 1 and Akt to the cell membrane, where they are phosphorylated and activated [78,79,80]. By off-target inhibition of TEC kinases, ibrutinib blocks upstream components of the aforementioned protective signaling pathway. Additionally, ibrutinib can directly or in-

directly inhibit the PI3K-p110δ subunit [3,13,90]. These inhibitory effects disrupt the PI3K/Akt signaling pathway, leading to insufficient phosphorylation of eNOS and reduced NO synthesis, ultimately resulting in impaired vasodilation while intensifying vasoconstriction, providing a direct pathophysiological basis for the development of hypertension [41,42].

Impairment of the PI3K/Akt/eNOS pathway promotes the release of inflammatory factors and exacerbates oxidative stress, further damaging vascular endothelial function [4]. In patients with arrhythmogenic cardiotoxicity, ibrutinib's inhibition of PI3K-p110δ is linked to vascular fibrosis and structural remodeling within cardiovascular tissue [3]. Reduced activation of PIK3CA is associated with increased susceptibility to atrial fibrillation and deterioration of cardiac conduction [91,92], which partly explains the high incidence of cardiovascular events during ibrutinib treatment. Based on preclinical studies, ibrutinib induces cardiovascular toxicities—including atrial fibrillation, left atrial enlargement, fibrosis, and inflammation—by inhibiting the PI3K/Akt pathway, which typically protects the heart under cardiac stress. In mouse models, 4 weeks of ibrutinib treatment can induce atrial fibrillation, left atrial enlargement, myocardial fibrosis, and inflammation, whereas the more selective acalabrutinib lacks these side effects. Accumulating evidence confirms that the PI3K/Akt pathway is a core regulator of blood pressure;restoring its activity can partially reverse the hypertensive phenotype [93,94]. Mechanistically, it is proposed that ibrutinib induces hypertension by inhibiting this pathway, which represents a key driver of its cardiovascular toxicity.

4.2.2 Inhibitory Effect of ITK

The off-target inhibition of *ITK* by BTKI (especially the first-generation drug ibrutinib) is an important mechanism for its induction of hypertension. As a core member of the TEC family of non-receptor tyrosine kinases, *ITK* plays a key role in the T-cell receptor signaling pathway and regulates NF-κB activation through multiple pathways [95].

The inhibition of *ITK* disrupts immune balance by skewing the T helper 17 cell (Th17)/regulatory T cell (Treg) cell balance through the Ca^{2+} signaling pathway; while it reduces Th17 cell populations, the resulting Treg-like cells exhibit impaired anti-inflammatory function [95]. In $ITK^{-/-}$ mice, the secretion of interferon gamma and TNF-α in T cells increases by approximately 2-fold, whereas secretion of the anti-inflammatory factor IL-10 decreases by about 50%. This Th1/Th2 imbalance and resulting inflammatory cytokine environment further reduce the activity of eNOS in vascular endothelial cells and damage vascular endothelial function [96].

In the $ITK^{-/-}Btk^{-/-}$ double gene knockout mouse model, lipopolysaccharide (LPS) stimulation leads to a 2.5-fold increase in NF-κB nuclear translocation and a 3-fold increase in the secretion of TNF-α and IL-6, ultimately resulting in increased blood pressure of approximately 2–25 mmHg [97]. These findings demonstrate that *ITK* and *BTK* negatively regulate LPS-induced inflammatory responses, inhibiting the TLR4-NF-κB pathway to suppress inflammation and ET-1 release. When these kinases are absent, excessive NF-κB activation causes a burst of pro-inflammatory factors and increases blood pressure via the ET-1 pathway [97].

Abnormal activation of the NF-κB pathway is a critical factor in BTKI treatment. Physiologically, NF-κB maintains homeostasis by regulating immune responses, inflammatory reactions, and cell metabolism, while promoting immune tolerance to prevent autoimmune damage [98,99,100,101]. Under pathological conditions, its abnormal activation can drive excessive secretion of inflammatory factors, damage vascular endothelial function, and promote the development of hypertension [102,103]. BTKI treatment exhibits a complex, two-sided effect on NF-κB pathway regulation: while it typically inhibits the pathway—evidenced by reduced BTK expression and cytoplasmic p65 accumulation [5]—it can also drive BTK-independent NF-κB activation via mutations in the caspase recruitment domain family member 11 coiled-coil domain, resulting in treatment resistance [46]. Furthermore, in some patients, inactivating mutations or deletions of the key negative NF-κB regulator, TNF-α-induced protein 3, lead to persistent signaling and poor ibrutinib response [45].

Animal studies confirmed the proposed mechanism: ibrutinib-treated mice (10 mg/kg/d, 4 weeks) exhibited a blood pressure increase of 15–20 mmHg, elevated plasma ET-1 levels, and reduced NO, whereas mice treated with the highly selective, weak ITK inhibitor acalabrutinib showed no significant blood pressure changes [104]. *In vitro* studies showed that 1 μM ibrutinib induced an approximately 80% reduction in T-cell ITK activity, while doubling ET-1 release from mast cells. Clinical data have shown that the incidence of ibrutinib-related hypertension in patients with CLL is as high as 14% to 30%, with a median onset time of 4.6 months, significantly higher than that of second-generation BTKIs [3]. In patients treated with ibrutinib, the degree of *ITK* inhibition is positively correlated with the increase in blood pressure ($r = 0.68$, $p < 0.01$), and the development of hypertension is closely related to an increased risk of cardiovascular adverse events [3].

4.3 Renin–Angiotensin–Aldosterone System-Renin/Angiotensin II Type 1 Receptor Signaling Pathway

BTKI may cause hypertension through the renin–angiotensin–aldosterone system (RAAS)-renin/angiotensin II (AngII) type 1 receptor (AT1R) signaling pathway. Accumulating clinical observations suggest that BTKI therapy, such as with ibrutinib, causes overactivation of the RAAS. Mechanistically, it is proposed that ibrutinib inhibits BTK in juxtaglomerular (JG) cells, disrupting the

PLCγ-IP_3-Ca^{2+} signaling axis. These disruptions block Ca^{2+} release from the sarcoplasmic reticulum, reducing cytoplasmic Ca^{2+} concentration in JG cells. This reduction in intracellular Ca^{2+} concentration removes the normal negative feedback on renin secretion and activates β1-adrenergic receptors, promoting the massive conversion of prorenin to active renin. this signaling cascade may result in elevated plasma renin activity [105] and elevated AngII levels.

AngII is a biologically active octapeptide in the RAAS system. An increase in its level can cause cardiac remodeling and plays an important role in the development of hypertension [106,107,108]. AngII binds to the AT1R, triggering Gq protein coupling and activating PLCβ, leading to the increased production of IP_3 and DAG. Cryo-electron microscopy structural analysis revealed that BTKI-induced increases in renin promote sustained AngII binding to AT1R, stabilizing the active conformation of AT1R and enhancing its bias towards Gq signaling activation, further amplifying the downstream signal transduction effect [109].

4.4 NOX-ROS Oxidative Stress Signaling Pathway

The NOX family is a class of proteins that transfer electrons across biological membranes, with family members including NOX1, NOX2, NOX3, NOX4, and NOX5 [110]. Their core biological function is to participate in the production of ROS [111]. Current evidence indicates that excessive activation of NOX is one of the most important mechanisms for ROS production [112]. NOX functions as an alternative, non-bacterial antibiotic mechanism by selectively generating ROS to neutralize bacterial virulence factors [113]. However, if ROS levels surge or cellular antioxidant defenses (e.g., glutathione system, superoxide dismutase enzyme activity) become overwhelmed, an oxidative stress state occurs [114], pushing the redox balance toward oxidation and causing widespread cellular damage. Excessive ROS triggers acute molecular damage by directly attacking nucleic acids, proteins, and lipids. This is followed by sustained ROS production from enzymes such as myeloperoxidase and NOX, which activate inflammatory pathways such as NF-κB. This cycle establishes a chronic inflammatory microenvironment that leads to vascular endothelial dysfunction, ultimately driving the progression of cardiovascular diseases such as atherosclerosis [115,116,117,118].

At present, the specific connection between BTKIs and NOX and ROS remains unclear, but BTKIs are closely related to the RAAS. AngII binds to the AT1R to promote ROS production [119,120,121,122], and BTKIs may cause hypertension through this pathway. Additionally, studies have found that in the absence of *BTK*, neutrophils stimulated by TLRs produce excessive ROS, which is closely related to the activation of NOX [6]. The specific mechanism requires further research for confirmation (Fig. 4).

5. Individual Susceptibility of Patients and Risk-Modifying Factors

The risk and severity of BTKI-related hypertension vary significantly among individuals, largely driven by baseline clinical characteristics and genetic polymorphisms. A thorough understanding of these factors is crucial for early risk identification, stratified management, and personalized prevention and treatment.

5.1 Genetic Susceptibility: Gene Variations of Core Molecules

5.1.1 Notch3 Polymorphism

As a key regulator of VSMC phenotypic transformation and vascular remodeling, *Notch3* gene polymorphisms can alter the activity of signaling pathways [123], thereby amplifying the pathological effects of BTKIs. Clinical cohort studies have shown that in patients diagnosed with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, the *Notch3 R544C* variant is significantly positively correlated with the risk of hypertension. After adjusting for covariates such as age and sex, the risk of hypertension in *R544C* variant carriers is 4.21 times that of non-carriers [124]. BTKI-induced hypertension may be related to *Notch3* gene polymorphism, specifically through a mechanism where these variants enhance the binding affinity of *Notch3* for its ligand Jagged1 [49].

5.1.2 PCSK9 Functional Gain-of-Function Variants

Gain-of-function variants of *PCSK9* (e.g., *R46L* and *D374Y*) significantly increase the risk of hypertension by exacerbating lipid metabolism disorders and inflammatory responses. These variants increase baseline LDL-C levels by enhancing the binding stability of PCSK9 to LDL-R [53] and activate the TLR4/NF-κB pathway, promoting the release of pro-inflammatory factors such as IL-1β and TNF-α [55,56]. Studies have shown that the *PCSK9 R46L* variant is significantly associated with a reduction in LDL-C levels by 11% to 16% in the general population (aged 20–80 years) [125]. Another study found that there were statistically significant differences in the *R496W* and *D374Y* mutations between patients with primary dyslipidemia and the control group (χ^2 = 10.742, p = 0.005; χ^2 = 6.078, p = 0.048). In primary dyslipidemia, patients heterozygous for the *R496W* mutation showed triglyceride levels 12.8 times higher (p = 0.015), while those with the *D374Y* mutation showed levels 3.4 times higher (p = 0.03) compared to patients with mutant and wild-type forms. In the entire study group (n = 401), the levels of total cholesterol (p = 0.021), triglycerides (p = 0.0001), high-density lipoprotein cholesterol (p = 0.028), and LDL-C (p = 0.028) were significantly elevated in carriers of the *PCSK9 R496W* and *D374Y* mutations [126]. BTKIs can induce free fatty acid metabolic disorders [58]. When combined with gain-of-*PCSK9* variants, it can cre-

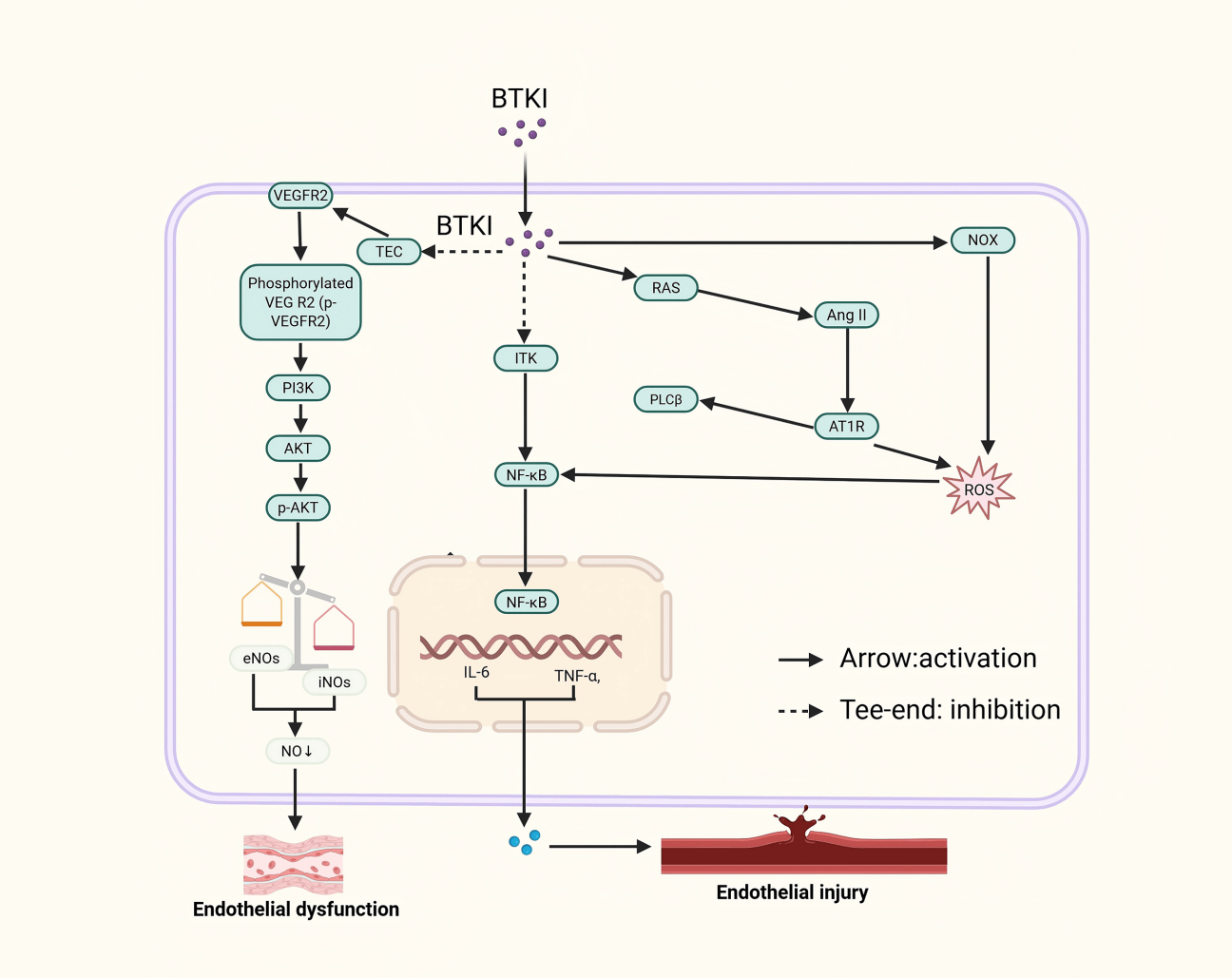

Fig. 4. Molecular mechanism by which BTKIs induce endothelial dysfunction and injury. After BTKIs inhibit *BTK*, on the one hand, it affects the *VEGFR2*-PI3K/Akt pathway mediated by TEC, reducing the generation of phosphorylated Akt (p-Akt), thereby inhibiting the activity of eNOS and leading to a decrease in the synthesis of vasodilator NO. On the other hand, BTKI can promote the accumulation of ROS through the RAS-NOX pathway and activate the NF-κB pathway to enter the nucleus, regulating the expression of inflammatory factors such as TNF-α and IL-6. The above changes (insufficient NO, excessive ROS, and release of inflammatory factors) collectively cause endothelial dysfunction, ultimately leading to endothelial injury (Chart source: BioRender.com; Date of creation: January 31, 2026).

ate a synergistic cycle of lipid dysfunction, inflammation, and endothelial damage, significantly increasing the risk of hypertension.

5.1.3 eNOS Gene Variation

eNOS generates NO through the oxidation of L-arginine. As a free radical, NO participates in vascular dilation and the regulation of vascular tone [127,128]. Studies on *eNOS* knockout mice have shown significant hypertension, confirming the importance of NO in blood pressure regulation [129,130]. A study of 152 healthy young individuals found that the *eNOS T-786C* polymorphism was significantly associated with blood pressure variability, whereas the *G894T* polymorphism showed no significant effect. Moreover, there was linkage disequilibrium between the two single-nucleotide polymorphisms, suggesting that their combined effect may have a significant impact on blood pressure variability [131]. A population study of Brazilian women indicated that the TT polymorphism of the *eNOS* gene *G894T* was significantly associated with the prevalence of hypertension and was an important risk factor for the disease, especially in elderly and overweight individuals [132].

5.2 Clinical Baseline Characteristics

Beyond genetic factors, clinicians must evaluate baseline characteristics, as pre-existing hypertension, diabetes, obesity, or chronic kidney disease can leave the vascular

system barely compensated. BTKI treatment acts as a "second hit", likely exceeding the threshold for cardiovascular homeostasis and triggering or worsening hypertension [28]. Due to age-related vascular changes, older patients are more sensitive to increased vascular resistance caused by BTKIs [27], which exacerbates their risk of developing hypertension.

5.3 Clinical Significance of Risk-Modifying Factors

Investigating risk-modifying factors has paved the way for the precise management of BTKI-related hypertension. Pre-treatment genetic screening for core variations in *Notch3*, *PCSK9*, and *eNOS* improves risk stratification, allowing for the early identification of high-risk patients. This enables proactive management, such as more frequent blood pressure monitoring (e.g., once or twice a week) and early preventive interventions, including strict low-salt diets or combined statin therapy [3]. In terms of individualized treatment, *PCSK9* gain-of-function variant carriers may benefit from the addition of PCSK9 inhibitors such as evolocumab [125]. Individuals with *eNOS* uncoupling variants may experience enhanced therapeutic benefits from combining antioxidants (e.g., vitamins C/E) with nuclear factor erythroid 2-related factor 2 (Nrf2) activators [131]. Ongoing investigations should prioritize the prospective clinical validation of integrated multi-gene models. Simultaneously, studies should examine the complex interplay among gene variations, BTKI classes, and management protocols to enhance both cardiovascular safety and oncological outcomes.

6. Management Strategies for BTKI-Related Hypertension

The management of hypertension induced by BTKIs (e.g., ibrutinib and acalabrutinib) should be based on the severity of blood pressure elevation and overall health status of the patient, with the goal of maintaining anti-tumor efficacy while safeguarding cardiovascular safety. This approach necessitates multidisciplinary collaboration and dynamic individualized adjustment [133].

6.1 Hierarchical Management Plan

For mild hypertension (blood pressure of 140–159/90–99 mmHg), the primary focus should be on lifestyle adjustments such as a low-salt diet, regular exercise, limited alcohol intake, and smoking cessation, with close monitoring of blood pressure. If blood pressure remains uncontrolled after 3–4 weeks, antihypertensive drug therapy should be initiated, with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) as the first choice. Their inhibition of the RAAS system may partially alleviate BTKI-related oxidative stress and endothelial dysfunction [133].

For moderate to severe hypertension (≥160/100 mmHg), drug therapy should be initiated immediately, and a calcium channel blocker (CCB) (e.g., amlodipine) or low-dose thiazide diuretic (e.g., hydrochlorothiazide) can be combined to synergistically reduce peripheral resistance and blood volume. If the patient has concomitant coronary heart disease or heart failure, beta-blockers (e.g., metoprolol) are preferred, but the potential side effect of increasing fatigue should be noted [133].

For patients with resistant hypertension who cannot discontinue BTKI, treatment options include adding aldosterone receptor antagonists (e.g., spironolactone) or direct vasodilators (e.g., hydralazine). Additionally, clinicians should evaluate whether to adjust the BTKI dosage or switch to a more selective, second-generation drug such as acalabrutinib [40].

In cases of hypertensive emergency (blood pressure ≥180/120 mmHg with evidence of target organ damage), intravenous antihypertensive treatment such as nicardipine or labetalol should be immediately initiated, and BTKI should be suspended until the patient is stable [133] (Fig. 5).

6.2 Emerging Intervention Programs

Among the current strategies, PCSK9 inhibitors (e.g., evolocumab, alirocumab, and teplizumab) and the small-interfering RNA (siRNA) drug inclisiran have garnered significant attention due to their unique lipid-lowering and vascular protective effects [125,134]. PCSK9 inhibitors significantly reduce serum LDL-C levels by blocking the binding of PCSK9 to LDLR and decreasing LDLR degradation, thereby improving vascular endothelial function and indirectly alleviating the progression of hypertension [135,136]. Inclisiran, as a long-acting PCSK9-targeting siRNA drug, blocks protein synthesis by degrading PCSK9 mRNA in the liver, achieving a reduction of over 50% in LDL-C levels in the Chinese population. Its ultra-long-acting characteristic (administration every 6 months) and low risk of drug interactions (not dependent on CYP450 metabolism) make it particularly suitable for patients with cancer who require long-term multidrug combination therapy [134,137].

7. Potential Therapeutic Strategies and Prospects

BTKIs induce hypertension through a multifaceted mechanism involving endothelial dysfunction, oxidative stress, and systemic inflammation. The *PCSK9/Notch3* pathway, as a key hub connecting lipid metabolism, inflammation, and vascular remodeling, provides a new entry point for mechanism-driven intervention strategies.

7.1 Interventions Targeting the PCSK9/Notch3 Pathway

Clinically, PCSK9 inhibitors (e.g., evolocumab and alirocumab) not only have lipid-lowering effects but also improve endothelial function [135]. Due to its minimal drug–drug interactions and semi-annual dosing character-

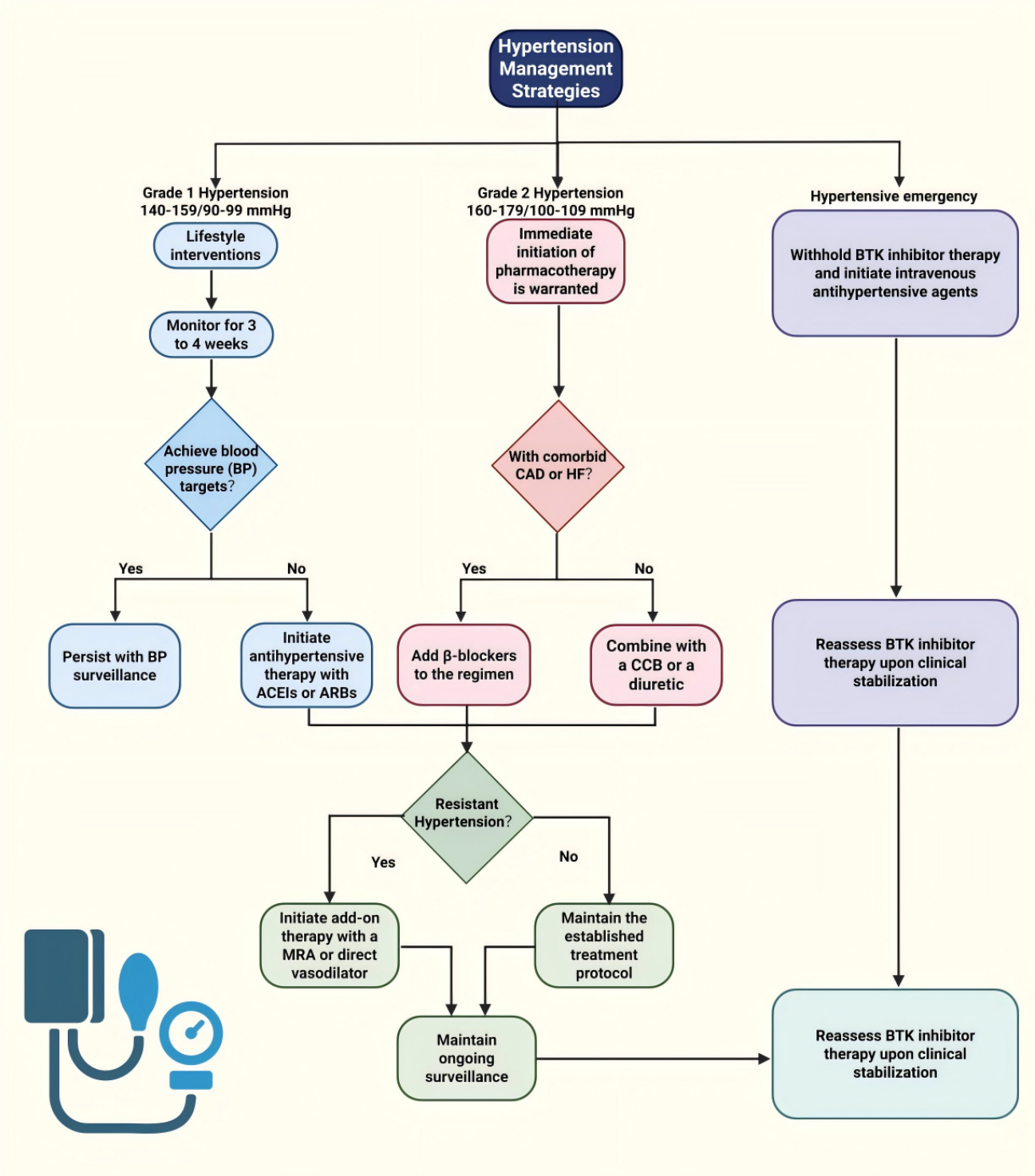

Fig. 5. Current management strategies for hypertension. For patients with grade 1 hypertension, lifestyle intervention is the first choice, followed by monitoring for 3–4 weeks. If the blood pressure target is not reached, drug treatment is initiated. For grade 2 hypertension, drug treatment is immediately started, and the choice of treatment regimen is based on the presence of complications such as coronary heart disease or heart failure. Angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) is the foundation, and a sequential combination with beta-blockers, CCB, or diuretics is adopted. In the case of a hypertensive emergency, BTKIs should be suspended and intravenous antihypertensive drugs should be used. All treatment paths require continuous monitoring. For refractory hypertension, mineralocorticoid receptor antagonist or direct vasodilators are added, and the risk of BTKIs use is reassessed after the condition stabilizes, thus forming a complete cycle strategy from assessment, intervention to long-term management. (Chart source: BioRender.com; Date of creation: October 5, 2025).

istics, the long-acting siRNA drug inclisiran is particularly suitable for patients with cancer [134]. Future prospective randomized trials are needed to evaluate the impact of this pathway-based intervention on blood pressure and vascular function.

7.2 Potential Value of Natural Compounds

Curcumin, a natural compound, shows significant promise in foundational research, driven by its multi-target regulatory capabilities and favorable safety profile. However, there is still a lack of direct clinical evidence for its application in BTKI-related hypertension. Existing literature is predominantly focused on the basic pharmacological and metabolic effects of curcumin, with a lack of targeted clinical trials for this specific patient population. Therefore, we hypothesize that due to its multi-target action and high safety profile, curcumin could serve as a promising auxiliary intervention for BTKI-induced hypertension.

Specifically, curcumin's potential as an adjuvant therapy is closely linked to its diverse mechanisms of action [138,139,140,141,142,143,144,145]. First, a major mechanism underlying BTKI-related hypertension is the drug's off-target inhibition of kinases such as TEC and *ITK*, resulting in the increased release of pro-inflammatory factors such as TNF-α and IL-6. Curcumin may reduce the generation of pro-inflammatory factors by inhibiting key inflammatory signaling pathways such as NF-κB and cyclooxygenase-2 [138,139], alleviating vascular inflammatory responses, and improving endothelial dysfunction. Second, curcumin may activate the Nrf2 antioxidant defense system [140,141], enhance the body's antioxidant capacity, reduce ROS damage to the vascular endothelium, reverse the downregulation of eNOS activity mediated by oxidative stress, and help restore NO production and vascular dilation function, which is highly consistent with the pathological features of enhanced oxidative stress in BTKI-related hypertension. Third, curcumin may regulate the expression level of *PCSK9* [142,143], optimize the lipid profile (such as reducing total cholesterol), reduce lipid deposition damage in the vascular wall, and simultaneously inhibit abnormal vascular proliferation by interfering with VEGF signaling, thereby reducing the increase in vascular resistance associated with BTKIs and indirectly assisting in blood pressure regulation. Finally, curcumin exhibits superior dose safety compared to natural drugs such as celastrol and resveratrol [144,145], making it an ideal candidate for combination therapy with BTKIs, as it reduces the risk of additional, unwanted side effects.

It is important to note that the above hypotheses are only based on theoretical deductions of the basic pharmacological effects of curcumin and the pathogenesis of BTKI-related hypertension, and thus need validation through prospective clinical studies. Future clinical trials should target patients with BTKI-related hypertension to establish optimal curcumin dosages, timing, and safety profiles. Furthermore, these studies should investigate curcumin's specific impact on blood pressure regulation, vascular function (including NO/ET-1 balance and endothelium-dependent dilation), and markers of inflammation and oxidative stress to validate its clinical utility.

7.3 Development of New BTK-Targeted Drugs

Protein degradation-targeting chimera (PROTAC) technology offers a novel strategy for development by degrading, rather than just inhibiting *BTK* activity, providing a distinct mechanism of action that may offer improved safety profiles. MT-802 represents a major breakthrough as the inaugural PROTAC molecule designed to degrade both wild-type and C481S mutant *BTK*. By recruiting the cereblon E3 ligase, it induces *BTK* ubiquitination and degradation via the proteasome pathway, demonstrating significant antiproliferative activity in ibrutinib-resistant CLL cell lines [146]. Notably, compared with ibrutinib, MT-802 exhibits higher kinase selectivity and significantly reduced off-target effects. This characteristic stems from its design based on a non-covalent ibrutinib scaffold, which is expected to enhance the degradation specificity for *BTK* and reduce adverse reactions caused by off-target inhibition, showing potential safety advantages [146].

7.4 Exploration of Alternative Treatment Options

In Phase I clinical trials for non-Hodgkin's lymphoma, the CD19-targeted antibody-drug conjugate (ADC) loncastuximab tesirine demonstrated encouraging single-agent anti-tumor activity and an acceptable safety profile [147]. Another study showed that no significant adverse event signals related to cardiovascular issues, such as hypertension or atrial fibrillation, were reported in the safety observation of related ADCs [148].

Chimeric antigen receptor (CAR) T-cell therapy is an important new immunotherapy for treating hematological malignancies that are resistant to traditional chemotherapy. However, a pharmacovigilance analysis based on World Health Organization VigiBase clinical reports indicated that CAR-T therapy is also associated with a series of cardiovascular-related adverse events. For example, in patients with DLBCL treated with Tisagenlecleucel, the mortality rate due to heart failure was 85.7% (6 of 7 deaths), and the mortality rate due to hypotension was 50.0% (27 of 54 deaths). In children with acute lymphoblastic leukemia, the mortality rates for cardiac arrest and heart failure were 100% (3 of 3) and 80.0% (4 of 5 deaths), respectively [149]. Overall, among the cardiovascular events reported for CAR-T products, hypotension had the strongest signal, followed by tachycardia and capillary leak syndrome. Given that such therapies do not cause hypertension, they may have potential applications in patients who are intolerant to BTKI due to hypertension.

8. Summary and Future Directions

BTKI-related hypertension is a key adverse reaction that affects the treatment continuity and cardiovascular safety of patients with cancer. The mechanism involves multiple pathways, primarily the abnormal activation of the *PCSK9/Notch3* axis, off-target inhibition of TEC/*ITK* kinases, overactivation of the RAAS system, and NOX-ROS oxidative stress. Together, these processes trigger endothelial dysfunction, vascular remodeling, and increased peripheral resistance. The genetic polymorphisms of patients (e.g., *Notch3*, *PCSK9*, and *eNOS* gene variations) and clinical baseline characteristics (such as underlying cardiovascular disease, advanced age, and obesity) further regulate the risk and severity of hypertension.

Currently, the management of BTKI-related hypertension mainly relies on traditional antihypertensive drugs (e.g., ACEI/ARB, CCB, diuretics); however, their efficacy is limited in some patients, creating an urgent demand for novel, mechanism-driven intervention strategies. While *PCSK9* inhibitors and natural compounds such as curcumin hold promise for therapeutic application, their long-term efficacy and safety profiles require validation through high-quality, rigorous clinical trials. New *BTK*-targeted drugs, such as PROTAC molecules like MT-802, offer a promising alternative for patients unable to tolerate traditional BTKIs. By utilizing a targeted protein degradation mechanism, these agents improve kinase selectivity and reduce off-target effects, potentially lowering the risk of cardiovascular side effects such as hypertension.

However, current evidence is primarily limited to basic research and retrospective data. In the future, the focus should be on: (1) verifying the activation status of the *PCSK9/Notch3* signaling in the vascular tissues of patients treated with BTKIs; (2) screening high-risk populations and biomarkers using omics technologies; and (3) designing prospective randomized trials to assess how mechanism-based interventions improve blood pressure and vascular health. Our research group is investigating how curcumin alleviates ibrutinib-related hypertension, specifically via the *PCSK9/Notch3* signaling pathway. In-depth analyses of the molecular mechanisms of BTKI-related hypertension and exploration of intervention strategies targeting *PCSK9/Notch3* will promote parallel advancements in cardiovascular protection and anti-tumor therapy, transforming precise cardiovascular management.

Author Contributions

BTL, JLL and KZ screened the literature. WJW and XQG contributed to conceptual refinement of the manuscript, provided critical revision suggestions, and assisted in literature interpretation, and BTL wrote the initial draft of the manuscript. QZ and JS performed literature collection and analytical sorting. All the authors have read and approved the final manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

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