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Review

B Cells at the Crossroads of Cardiovascular and Hematologic Disease: Paving the Way for Novel Immunomodulatory Therapies

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Abstract
The interaction between the immune and cardiovascular systems is a growing field of investigation with bidirectional aspects. B cells are modulators of the adaptive and the innate immunity and they orchestrate bone marrow and spleen immune responses beyond infectious diseases. B cell regulation contributes to the pathophysiology of myocardial damage in several conditions including myocardial infarction, heart failure and atherosclerosis. In parallel, B cell-derived hematological disorders are interlinked to cardiovascular complications, including thrombosis and immunoglobulin-related cardiotoxicity. The scope of this review is to summarize the function and role of B cells as important players in myocardial and vascular adaptations to injury and as mediators of cardiovascular adverse events in hematological disorders. The primary focus is to highlight the clinical and preclinical findings regarding B cell-targeted therapies and their positive or negative impact on the cardiovascular system. A deeper understanding of B cell subpopulations, functions, and secretome could lead to targeted therapeutic interventions for cardiovascular and hematologic diseases.

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1. Introduction

The adult human heart consists of a diverse population of roughly 5 billion cells which operate together within specialized tissue microenvironments (niches) to regulate each heartbeat [1, 2]. This intricate coordination is disrupted by conditions, including cardiovascular (CV) comorbidities, such as ischemic heart disease. Advances in single-cell technologies have uncovered the heterogeneity of lymphoid cell populations in both mice and humans, identifying distinct subsets with specialized functions. Previously underappreciated populations, including cardiac-resident or bone-derived hematopoietic stem cells (HSCs), mature B cells and plasma cells, can contribute to the development of heart diseases. Although, the role and function of each subset of the B lymphoid lineage remains to be fully elucidated, several data support their involvement in immune responses to myocardial injury and the increased risk of CV events observed in hematologic malignancies [3, 4].

This review focuses on the B and plasma cells bidirectional relationship with the CV system and is structured into four main sections. First, we provide an overview of the role and function of this lymphoid lineage from an immunological perspective. Next, we present a comprehensive summary of current findings regarding the involvement of B cells in the healthy and diseased myocardium. In the third section, we explore CV adverse events associated with hematologic malignancies. Finally, we examine existing pharmacological interventions targeting B cells and their effects on the CV system, aiming to suggest future directions for therapeutic strategies in both CV and hematologic diseases.

2. Maturation and functions of B cells

HSCs reside within the bone marrow and possess the capacity for self-renewal and multilineage differentiation, resulting in an approximate release of one trillion cells daily [5]. During lymphopoiesis, HSCs differentiate into common lymphoid progenitors (CLP), and lead to the origination of T and B cell lineages and natural killer cells [6]. HSCs mobilization is governed by interactions with stromal cells of the bone marrow niche, and signals such as macrophage colony-stimulating factor 1 (CSF1), granulocyte–macrophage colony-stimulating factor (GM-CSF) and cytokines [7].

B cell development occurs along with immunoglobulin (Ig) gene rearrangements. Progenitor B cells initiate the combinatorial rearrangement of the heavy chain (HC) (V, D, and J gene segments in the H chain locus) to differentiate into precursor B cells that express immature B cell receptors (BCR) with a surrogate light chain (LC)[8]. Rearrangement of the LC genes (V and J gene segments in the L chain loci) leads to their differentiation to IgM-expressing immature B cells and to IgM^+IgD^+ mature resting B cells. Ig gene rearrangement is prone to defects resulting in the development of B cell malignancies, immunodeficiencies or autoimmunity. Immature B cells exit the bone marrow and undergo their final stages of development in the spleen to form mature B cells [9] which comprise of distinct cell subsets: follicular B cells, marginal zone (MZ) B cells and B1 cells [10].

Follicular B cells are the dominant subset and reside within lymphoid follicles of the spleen and lymph nodes. Due to their location in follicles adjacent to T cell zones, they mount T helper-dependent responses to antigens presented by follicular dendritic cells (DCs) [11]. Follicular B cells proliferate and differentiate into antibody producing plasma cells or enter germinal centers, where affinity maturation of the BCR occurs [12].

MZ B cells, by contrast, are strategically placed in the interface between the red and white pulp in the spleen to respond to blood-borne pathogens and antigens. Their activation threshold is lower than follicular B cells, allowing IgM production in the absence of cluster of differentiation 40 (CD40)-dependent signals from follicular T helper cells. MZ B cells express polyreactive BCRs -which resemble the broad recognition of molecular patterns of toll-like receptors (TLRs)- and high levels of TLRs (like DCs, macrophages and granulocytes), allowing them to initiate low-affinity antibody responses prior to the induction of high-affinity antibody production by conventional follicular B cells [10, 13]. In mice, expression of CD1d and CD21 on MZ B cells facilitates the recognition of lipid antigens [14, 15], leading to the production of lipid-specific antibodies.

B1 cells are located in coelomic cavities such as the peritoneum and the lungs. They are spontaneously producing natural IgM antibodies without depending on thymus activation [16]. IgM is the earliest type of membrane-associated Ig expressed during B-cell ontogeny, it circulates as pentamer and is 1–2 mg/ml in the human blood. Besides host defense, IgM removes apoptotic cells and oxidized lipids from the circulation [17].

Mature B cells upon BCR activation give rise to plasmablasts -transient, proliferating cells that secrete antibodies [12]-, while plasma cells represent the terminal differentiation state of B cells and are specialized in high-rate antibody secretion. They are well distinguished from other populations due to the membrane expression of Syndecan-1 (CD138) which can also bind to fibronectin, collagen and basic fibroblast growth factor [18].

While B cells are traditionally recognized as antibody-producing cells, it is now well established that they contribute to immune regulation through a variety of mechanisms. They secrete a wide range of cytokines affecting other immune cells [19]. B cells express high levels of major histocompatibility complex (MHC) class II molecules, acting as antigen-presenting cells [20]. They recognize antigens through the BCR, internalize and process them, and subsequently present derived peptides to $CD4^+$ T cells, particularly within germinal centers [20, 21], a function that has also been recognized for MZ B cells in mice [11].

B cells shape immune responses through cytokine secretion, triggered by stimuli such as TLR activation and BCR engagement. These soluble mediators exert diverse effects: B cells enhance innate immunity through the production of interferon gamma (IFN-γ), interleukin (IL)-6, and IL-17 [19]; promote $CD4^+$ T-cell polarization; contribute to the development of lymphoid tissues through LTα1β2 [19]; mediate monocyte recruitment via C-C chemokine ligand 7 (CCL7) [22]; facilitate T-cell trafficking to inflamed tissues by secreting PEPITEM [23] and directly modulate T-cell function [24].

Conversely, certain B-cell subsets, referred to as regulatory B cells (Bregs), exert immunosuppressive functions. These cells secrete anti-inflammatory cytokines such as IL-10 contributing to immune tolerance and resolution of inflammation [19]. Bregs also promote regulatory T-cell (Treg) activity, preserve natural killer cell homeostasis, and suppress the pro-inflammatory activity of monocytes, DCs, and $CD8^+$ T cells [25]. In mice, IL-10-producing Breg subsets include $CD5^+CD1d^{hi}$ B (B10) cells, MZ B cells and their precursors, as well as plasmablasts and plasma cells [26]. In humans, comparatively fewer Breg subsets have been characterized among peripheral blood mononuclear cells (PBMCs). The immature $CD19^+CD24^{hi}CD38^{hi}$ B cell subset produces the highest levels of IL-10 along with plasmablasts, and plasma cells as in mice [26]. Their ontogeny is yet to be explored, but the balance of pro- and anti-inflammatory environments can account for the differentiation and expansion to regulatory rather than effector B cells.

Taken together, B cells originate from HSCs and undergo a stepwise developmental process initially in bone marrow and afterwards in secondary lymphoid organs, that ensures the generation of a diverse and functional BCR repertoire. Their maturation yields distinct subsets—follicular B cells, MZ B cells, and B1 cells—each occupying specialized anatomical niches and serving complementary roles in immune surveillance. Collectively, B cells are not only key producers of antibodies but also active participants in immune regulation through antigen presentation and cytokine secretion or by limiting excessive immune activation and promoting tolerance.

3. B cells in normal cardiovascular function and in disease

3.1 The presence and role of B cells in the healthy myocardium

Both B and T cells are part of the physiological immune cell landscape of the heart, even in the absence of disease in both humans and rodents [27]. By using single-cell and single nucleus technologies, Litviňuková et al. detected myeloid and lymphoid cells in humans consisting of approximately 10% and 5% of cardiac cells in the atrial and the ventricular regions, respectively [28]. In the same study, 8 subpopulations of lymphoid cells were identified including B cells and plasma cells which were shown to interact with cardiomyocytes and fibroblasts, deducing paracrine circuits important for cardiac homeostasis [28]. Immunohistochemistry using antibodies against the markers CD3, CD20, and CD31 on post-mortem cardiac biopsies from individuals without underlying cardiac pathology, indicated that $CD20^+$ B cells were present both in the interstitial (extravascular) and intravascular compartments, as well as across the myocardium and epicardium. The functional role of B cells in human heart is not fully understood, while gene expression analysis revealed that pathways related to "B-cell receptor signaling pathway," "Antigen processing and presentation," and "Cytokine-cytokine receptor interaction" were upregulated in cardiac B cells in comparison with peripheral B cells. Based on these, the authors hypothesized that B cells extravasate, degrade the extracellular matrix and crawl through the interstitial space where they communicate with other cells such as fibroblasts [29].

In a multi-omics approach, Kanemary et al. [30], identified cardiac plasma cells in the human epicardium in two niches; one enriched in lymphatic endothelial and immune cells, and in a fibroblast-rich niche. Gene expression analysis revealed that IgA and IgG expressing cells were distinctly localized, with IgA presence being pronounced in the subepicardial region [30]. Cardiac plasma cells expressed C-C chemokine receptor 2 (CCR2) and CXC chemokine receptor 4 (CXCR4) via which they can interact with endothelial cells, fibroblasts, and resident macrophages. Based on their transcriptome, plasma cells were predicted to interact with macrophages via B-cell activating factor (BAFF) receptors (BAFF-R). In the same study, endothelial, fibroblast and plasma cell interactions were mediated by transforming growth factor (TGF) signaling. These findings highlighted the important role of plasma cells in cardiac homeostasis, fibrosis and immune defense [30]. In parallel, Bermea et al. provided a functional explanation for the presence of B cells in the human heart [31]. They identified naïve B cells (i.e., B cells that have not been activated or encountered antigens) and plasma cells in the healthy heart which interacted with endothelial cells, fibroblasts, pericytes, and smooth muscle cells via non-canonical Wnt signaling and with other B cells, endothelial cells, and myeloid cells through PECAM1 homophilic interaction, probably participating in transmigration or survival [31]. In an integrated analysis of existing single-cell data, de Winter et al. identified the B cells subsets in the human heart, comprising B1 cells, naive B cells, plasma cells, memory B cells and Bregs, supporting the important role of B cells in cardiac homeostasis and immune tolerance [32].

Novel omics-derived data from humans corroborate previous observations in murine hearts, showing that B cell subsets exist in the heart. Kalikourdis group identified B cells in the healthy murine heart via single cell technologies and the expression of the B220 marker [27, 29], supporting the conservation of B cell subsets and function in the heart between humans and mice.

Interestingly, the neonatal heart also has B cell subsets to promote cardiomyocyte proliferation [33]. During transition to adulthood, the markets of B cells are altered, and naïve B cells have been shown to circulate between the heart and spleen throughout life but the functional significance of this equilibrium has not been identified [34].

3.2 The role of B cells in cardiovascular disease

Upon the seminal work of Adamo et al. [35] dated in 2020, we summarize the novel findings on the contribution of B cell subsets and Igs related to atherosclerosis, ischemic heart disease and heart failure (HF) (Fig. 1A-C).

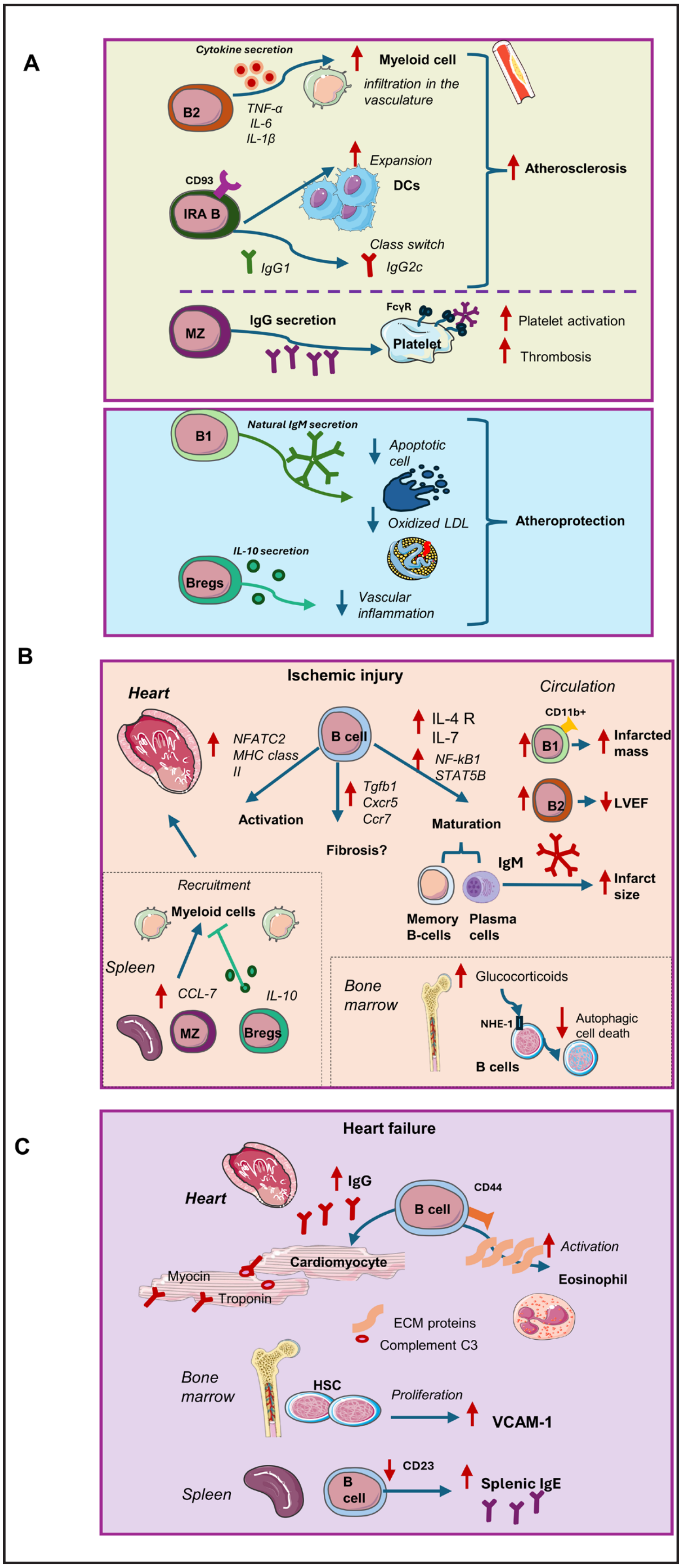

Fig. 1. Molecular mechanisms suggested for the interplay of B cells in cardiovascular disease. This Fig. summarizes the proposed mechanisms by which B-cell subsets contribute to cardiovascular pathology. A) In atherosclerosis, splenic B2 cells release proinflammatory cytokines that promote myeloid cell infiltration, increase vascular permeability, and amplify inflammation. IRA B cells expand DCs and enhance IgG class switching, whereas MZ B cells promote thrombosis through IgG-mediated platelet activation. These subsets may promote atherosclerosis. Conversely, B1 cells exert atheroprotective effects by producing natural IgM that recognizes oxLDL and apoptotic cells, while Bregs secrete IL-10, attenuating vascular inflammation. B) In ischemic injury, CD20$^+$ B cells are rapidly recruited after AMI, expressing genes linked to activation, fibrosis and differentiation into plasma and memory B cells. Antibody production (IgM, IgG) contributes to infarct size, partly through complement activation. Circulating CD11b$^+$ B1 cells correlate with larger infarcts, whereas B2 cells are associated with LVEF. splenic MZ B cells secrete CCL7, driving myeloid cell recruitment to the infarcted heart, an effect counteracted by IL-10–producing Bregs. Bone marrow B cells undergo glucocorticoid-driven autophagic death mediated by NHE1. C) In heart failure, HSC proliferation results in macrophage VCAM-1 upregulation. B cells interact with eosinophils via CD44, and IgG antibodies against myosin, troponin, or complement C3 are detected in the heart. Reduced CD23 expression increases splenic IgE levels, further amplifying inflammation. B regs: B regulatory cells; CCL/CCR: C-C chemokine ligand/receptor; CXCR:C-X- chemokine receptor, DCs: dendritic cells; ECM: extracellular matrix; FcγRs: Fc gamma receptors; HSC: hematopoietic stem cells; Ig: immunoglobulin; IL: interleukin; IRA: Innate response activator; LVEF: Left ventricular ejection fraction; MZ: marginal zone B cells; NHE1: sodium-hydrogen exchanger-1; NFATC-2: nuclear factor of activated T cells, cytoplasmic differentiation 2; oxLDL: oxidized LDL, TNF-a: tumor necrosis factor a, VCAM-1:vascular adhesion molecule -1.

3.2.1 Atherosclerosis

B cells have emerged as significant contributors to vascular inflammation, atherosclerosis, and thrombosis. They have been identified in human carotid atherosclerotic plaques [36] and their interactions with endothelial cells, platelets, and other immune components underscore their multifaceted involvement in vascular pathology.

Activated B cells secrete pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), IL-6, and IL-1β, which can induce endothelial cell-activation and dysfunction and in turn, increase monocyte and macrophage infiltration [37, 38]. This process is characterized by increased expression of adhesion molecules, enhanced vascular permeability, and a pro-thrombotic state, all of which are critical early events in atherogenesis and thrombosis. Furthermore, B cell-derived cytokines can promote the recruitment and activation of other immune cells, amplifying vascular inflammation. B cells can influence platelet function through the formation of immune complexes that engage Fc gamma receptors (FcγRs) on platelets. This interaction can lead to platelet activation, aggregation, and the release of pro-thrombotic mediators, thereby contributing to thrombus formation [37]. Additionally, B cell-derived antibodies can directly bind to platelet antigens, further modulating platelet activity and promoting a pro-thrombotic environment [39].

B cells also exhibit both protective and pathogenic roles in atherosclerosis, largely dependent on their subset classification. B1 cells produce natural IgM antibodies that recognize oxidized low-density lipoprotein (oxLDL) and apoptotic cells, facilitating their clearance, thereby exerting atheroprotective effects [40]. In contrast, B2 cells, comprising follicular and MZ B cells, promote atherosclerosis by producing pro-inflammatory cytokines and pathogenic IgG antibodies in *Apoe*$^{-/-}$ mice [41]. Bregs suppress immune responses through the production of IL-10 and have been implicated in the attenuation of atherosclerosis by modulating T cell responses and reducing vascular inflammation in a mouse model of systemic lupus erythematosus (SLE) and atherosclerosis [42].

The unique B-cell subsets and their role in atherosclerosis is still under investigation. For instance, depletion of B2 cells using anti-CD20 antibodies or BAFF receptor antagonists has been shown to reduce atherosclerotic lesion development in murine models [43]. A distinct subset of B1 cells—termed innate response activator (IRA) B cells—has been identified to respond to lipopolysaccharide (LPS) stimulation by secreting GM-CSF. IRA B cells are distinguished from conventional B1 cells as they express the immature B-cell marker CD93. IRA B cell deficiency in cholesterol-fed *Ldlr*$^{-}$/$^{-}$ mice resulted in reduced atherosclerosis [44]. IRA B cells can promote mature DC expansion, leading to increased IFN-γ–producing T helper cells and a class switch from IgG1 to IgG2c antibodies directed against oxLDL which enhances pro-atherogenic immune responses. Notably, IRA B cells were found at higher levels in the spleens of patients with symptomatic cardiovascular disease (CVD) compared with those with asymptomatic disease, suggesting their potential role in disease progression [44].

3.2.2 Post-ischemic myocardial injury

Cardiomyocyte necrosis and microvascular damage release intracellular components activating neutrophils, monocytes, and macrophages [32]. CD20^{+} B cells in patients and B220^{+}IgM^{+} B cells in mice are recruited early after acute myocardial infarction (AMI) in the heart, contributing to innate and adaptive immune response to AMI via antibody-dependent and independent mechanisms.

In patients within 6 hours of AMI, B cells account for approximately 7% of PBMCs [45]. Single-cell RNA sequencing highlighted that in both immature and mature B cells, chemokine signaling and immunometabolism were affected. Notably, mature B cells in patients with fibrous plaque rupture had markedly elevated expression of the IL-4 receptor and the levels of IL-7, suggesting their activation and cytokine production [45]. In another study in patients, upon thrombolytic therapy for AMI, circulating CD11b^{+} B1 cells correlated to the infarcted mass and B2 cells (CD19^{+}CD20^{+}CD43^{-}) remained independent predictors of left ventricular ejection fraction (LVEF)[46]. In parallel, in patients with AMI, a pertained increase of IgG was observed that can trigger antigen-specific adaptive immune responses, contributing to sustained injury but these IgG epitopes require further investigation [47]. Tan et al. analyzed the proteins interacting with Igs in patients with AMI and chronic stable coronary syndrome. They revealed that the Igs' proteome landscape included factor X, which was validated as target of the AMI related B cell repertoire. Moreover, immunoglobulin-associated proteome (IgAP) was related to the pathways of complement activation and cholesterol metabolism [48].

In mice, an increased proportion of activated (CD69$^+$) B cells in the myocardium was detected from the 3rd day to 1 week post-AMI, and a similar increase was observed in the spleen and the peripheral blood at days 3 and 5. Also, at day 5 the expression of TNF-α, IL-1β, IL-6, TGF-β1, and BAFF was the highest in the myocardium, spleen and peripheral blood with the most obvious myocardial inflammatory cell infiltration [49]. Early post-AMI, in both mouse and human hearts, B cells showed increased expression of transcription factors related to their activation. These included nuclear factor of activated T cells, cytoplasmic differentiation 2 (NFATC2) and MHC class II gene expression, which were normalized at later stages (28 days) [32]. Long-term post-AMI, maturation and memory B cell formation genes were upregulated (i.e., NF-κB1 and STAT5B) in parallel with genes relative to plasma cell maturation and antibody production [32]. This study also reported the existence of collagen-producing B cells supporting the role of B cells in fibrosis [32].

B cell knock-out mice demonstrated decreased fibrosis in parallel to decreased gene expression levels of cytokines and fibrosis markers (i.e. TNF-α, IL-1β, IL-6 and TGF-β1) in the myocardial tissue and the peripheral blood, but the exact cell origin of these cytokines was not defined [49]. Heinrichs et al. showed that B cell populations increased up to the 7th day post AMI in the scar area in the murine heart [50]. Heart B cells uniquely expressed *Tgfb1* and *Cxcr5* and *Ccr7* receptors compared to B cells from the lymph nodes. Antibody-mediated neutralization of CXCL13 was performed and when C*xcr*$^{-/-}$ mice were employed, B cell recruitment and cardiac *Tgfβ1* expression was ameliorated [50]. Ultimately these strategies had a neutral effect on cardiac function and morphology post AMI, questing the role of B cells as a source of TGF-1 mediated fibrosis.

Clonal expansion of B cells in lymph nodes and natural IgM infiltration in the heart, as observed in mice, [50] could account for a future strategy to target B cells in AMI. Natural IgM antibodies contribute to the myocardial infarct size. Mice bearing either a selective (*Cr2*$^{-/-}$) or total deficiency (*RAG-1*$^{-/-}$) in IgM demonstrated reduced infarct size which was comparable to wild type mice when IgM was injected [51]. Besides the heart, the role of splenic MZ B cells was highlighted in AMI mice with permanent ligation. Sun et al. demonstrated that miR21 or *Hif1a*-specific deletion from MZ cells ameliorated cardiac function [52]. They also proved that miR21/HIF-1α signaling in MZ B cells results in TLR-dependent CCL7 expression which leads to inflammatory monocyte recruitment in the ischemic myocardium [52].

Despite several reports of the contribution of B cells in myocardial damage, specific B cell subsets have favorable effects on cardiac function. Intramyocardial injection of B-lymphocytes early post-infarction in rats resulted in preserved LVEF and amelioration of apoptosis [53]. This population was CD45RA$^+$ and comprised mainly immature and mature B cells [53], suggesting that non-activated immature B cells can have a protective role. In parallel, B cells can interact with neutrophils leading to their phagocytosis from macrophages *in vitro* and *in vivo*, which overall confers a cardioprotective effect [54]. Bregs possess anti-inflammatory effects, although the exact mechanism mediating this effect is not fully elucidated [55]. In a small cohort of patients after AMI, circulating levels of CD24^{hi}CD38^{hi} Bregs, but not of CD24$^+$CD27$^+$ B10 cells, were reduced compared to stable angina pectoris, suggesting the role of Bregs in inflammation upon plaque rupture and thrombi formation [56]. In the pericardial fat of murine hearts, IL-10 producing Bregs attenuated monocyte recruitment and IL-10 depletion led to exacerbated myocardial injury and function [57]. A therapeutic strategy that was shown to increase Bregs subsets is via low doses of IL-2 in patients with type 1 diabetes or BACH2 suppression in murine and human isolated B cells [58].

Hu et al. reported that AMI stimulates glucocorticoid release from the neuroendocrine system, inducing sodium-hydrogen exchanger-1 (NHE1)-mediated autophagic death of bone marrow B cells, accompanied by reduced lineage commitment, activation, and antibody production, while splenic B cells expanded [59]. In the same study, the authors suggested that the sodium glucose co-transporter-2 (SGLT-2) inhibitor empagliflozin which has cardioprotective effects [60–62], preserves the bone marrow naïve B cell populations [59]. These results are in line with the myocardial structural and functional improvements 72 hours post-AMI by the infusion of bone marrow (but not spleen or blood)-derived B cells into C57BL/6J mice prior to MI induction [59]. Empagliflozin reduced myocardial infiltration of Ly6C^{hi} inflammatory monocytes and neutrophils in AMI mice [60], attenuated the percentage of myeloid cells in the spleen, and in parallel reduced cardiac GM3 gangliosides which induce immune cell recruitment in a TLR-dependent manner [63]. Empagliflozin also reduced circulating white blood cell-counts in diabetic-AMI patients [60],altogether bringing the immune-heart axis in the forefront of the suggested cardioprotection by SGLT-2 inhibitors.

3.2.3 Heart failure

In the failing heart of patients, microarray data reported increased myocardial infiltration of memory B cells, which produced antibodies, cytokines and chemokines involved in the development of HF [64]. In the peripheral blood, increased CD19$^+$ or TNF-producing cells have been reported for HF patients [29]. The functional role of cardiac B cells has been investigated in the context of dilated cardiomyopathy (DCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC) in humans by the group of Bermea et al. [31]. In ARVC, the interaction of B cells with other populations was reduced compared to healthy hearts. In DCM, an increased interaction with macrophages, monocytes, cardiomyocytes, and endocardial cells was observed, possibly through the activation of the phosphoinositide 3-kinase (PI3K) pathway. B cell communication with fibroblasts, epicardial fat cells, and other stromal cells was increased via the interaction of extracellular matrix proteins, such as laminin, collagen, and fibronectin with CD44 on B cells. In the same study, eosinophils interacted with B cells through the CD44/CD74 complex, which activates NF-κB signaling, suggesting that B cells play a role in eosinophil activation in DCM.

Rats with HF with reduced ejection fraction (HFrEF) of ischemic origin have elevated mature IgG isotypes in their circulation targeting myosin, troponin or complement component (C)3. Similarly, IgGs and C3 heart depositions were evident in HF patients in the perivascular and interstitial space [65]. Martini et al. suggested that cardiac B cells are activated and expanded in a murine model of pressure overload (transverse aortic constriction, TAC) [66]. B cells clustered together but failed to organize in follicles despite the expression of *Cxcr5*. The role of auto-antibodies is highlighted by the study of Smolgovsky et al. [67]. in which, TAC results in protein modifications with isolevuglandins (lipid peroxidation products) and in B cell responses with the production of anti-isolevuglanin antibodies. These effects were not replicated in HF with preserved ejection fraction (HFpEF). Recently, in a TAC mouse model, Feng et al. [68]identified that splenic IgE$^+$ B cells are elevated due to the reduction of CD23, which negatively regulates IgE$^+$ production. A key mediator for this process was lactotransferrin which is released by the heart [68]. HF patients have also increased IgE levels.

The role of inflammation in HFpEF patients is appreciated based on conventional markers [i.e., high-sensitivity C-reactive protein (hs-CRP), IL-6] that predict morbidity and mortality, but whether this immune activation is directly related to B cell functions is ill-defined.

The main driver of HFpEF is hypertension. Guzik at al. [69], reviewed the immunological aspects observed in hypertension. Angiotensin II infusion leads to increased splenic B cells and plasma cells in mice, in parallel with augmented circulating and aortic IgG. B cell depletion or BAFF receptor deficiency attenuated hypertension, aortic accumulation of macrophages and stiffening [70]. However, the role of Ig production has been debated since global B cell or IgM deficiency did not result in the attenuation of hypertension [71]. Yet, in an angiotensin-

II-induced HF mouse model, B-cell absence resulted in preservation of the cardiac function, attenuation of hypertrophy and collagen deposition in parallel with reduced IgG deposition [72].

In patients with diastolic dysfunction, elevated circulating levels of IgG1 and IgG3 were detected which corroborated with cardiac remodeling [73]. HSC proliferation via metabolic regulation of neighboring myeloid cells has been identified as a driver of HFpEF, leading to the modulation of macrophage adhesion molecule *Vcam1* in a murine 2-hit model of HFpEF that incorporates obesity and hypertension [74]. Of note, β2-microglobulin, a component of MHC class I which is elevated in patients with B cell malignancies, has been found elevated also in patients with pulmonary hypertension and HFpEF predicting disease severity [75]. HFpEF was also associated with decreased lympagiogenesis and lymphatic endothelial cells in mice and patients [76]. The possible relation of these findings to B cell regulation remains to be elucidated.

In summary, in the healthy myocardium, B cells, including naïve, memory, B1, plasma cells, and Bregs, reside in interstitial, intravascular, myocardial and epicardial compartments, interacting with endothelial, stromal cells and macrophages that support tissue surveillance, yet more roles are soon to be clarified. In CVD, B cells exert subset- and condition-specific effects. In atherosclerosis, B1 cells and Bregs provide atheroprotection, while B2 and IRA B cells promote inflammation, pathogenic IgG responses and a pro-thrombotic environment (Fig. 1A). In post-ischemic myocardial injury, B cells are early recruited and activated, contributing to cytokine production, fibrosis and antibody-mediated tissue damage, while cardioprotection via Bregs and immature B cells has been reported (Fig. 1B). In HF, B cells participate in maladaptive remodeling through cytokine production, autoantibody generation, and interactions with cardiomyocytes, eosinophils, macrophages, and stromal cells (Fig. 1C). Their exact role in HFpEF remains less clearly defined. Overall, B cells serve as a promising target for therapeutic modulation in CVD since B cell depletion or modulation could mitigate inflammation, hypertrophy, and functional decline.

4. Cardiovascular disease in B cell-related hematologic malignances

Most B-cell hematologic malignancies are linked with increased CV risk due to a complex interplay of disease, treatment and patient-related factors.

Multiple myeloma (MM), a plasma cell malignancy with monoclonal protein secretion, predominantly affects the elderly—who are already at higher baseline CV risk. Up to 7.5% of MM patients experience CV events such as HF, arrhythmias, or ischemia [77, 78]. MM is frequently associated with–CV comorbidities, influenced by both disease-related and treatment-related factors. For instance, anemia and renal dysfunction are independent predictors of CVD, and hypercalcemia can predispose to arrhythmias.

Venous thromboembolism (VTE) is a common and serious complication associated with MM or its treatment. VTE rates range from 4% - 16%[79] and MM patients have a 9-fold increased risk of VTE compared to the general population. In patients with MM, monoclonal protein has been linked to hyperviscosity, hyperfibrinogenemia, decreased protein C or S activity, impaired fibrinolysis and interferes with coagulation. In parallel, elevated IL-6 and TNF-α, as well as plasma cell-derived extracellular vesicles cause endothelial cell and platelet activation [80]. Therapy-related factors contribute significantly to the risk observed, like corticosteroids, proteasome inhibitors (PIs) [81, 82], high-dose melphalan, immunomodulatory drugs (IMiDs) [83, 84] and novel agents such as cellular therapies [85, 86]. IMiDs in particular, increase significantly the risk of thrombosis [87, 88].

Waldenström's macroglobulinemia (WM), defined as a lymphoplasmacytic lymphoma with IgM paraproteinemia, is associated with a 2–4-fold elevated VTE risk [89] but not with arterial thrombosis risk. IgM-related hyperviscosity impairs microcirculation and promotes thrombosis through red cell aggregation and clotting factor interference [90, 91]. Inflammatory cytokines and elevated FVIII levels exacerbate the prothrombotic environment [92, 93].

Monoclonal gammopathy (MG) is characterized by the presence of a monoclonal protein produced by a low-grade plasma or B-lymphocytic clone. Monoclonal gammopathy of undetermined significance (MGUS) is present in 3.2% of Caucasians aged 50 years [94, 95], an incidence that increases with age [96]. Many studies have demonstrated an association between MGUS, CV risk [97, 98] and VTE risk [97], but the link is mostly epidemiological. The recent iSTOPMM study evaluated patients with "screened", rather than "clinical MGUS" and confirmed a 1.3-fold increased VTE but not arterial thrombotic risk [99]. Studies on biomarkers suggested possible shared biologic features between MM and MGUS like platelet activation and hypercoagulability [100, 101]. The term Monoclonal Gammopathy of Thrombotic Significance (MGTS) [102] has been introduced to describe patients presenting with clinically significant thrombotic complications linked to the M-protein with uncommon thrombogenic properties, such as anti-platelet factor 4 activity but otherwise no overt malignancy [103, 104].

Excessive production of LCs by plasma cells and their deposition as amyloid fibrils in various organs comprises the clinical entity of light chain (AL) amyloidosis, which is a separate but related condition that results in cardiac involvement. In AL amyloidosis, a low-grade clonal plasma or B cell population produces amyloidogenic free LCs that aggregate to form insoluble fibrils, which deposit in tissues causing organ dysfunction [105]. Over 75% of patients have cardiac involvement at diagnosis [106]. Even in the prefibrillar state, the amyloidogenic LCs (λ subtype in 80%) induce cardiotoxicity and increase cellular oxidative stress in human heart cells [107]. Amyloid infiltration results in ventricular wall thickening, diastolic dysfunction (initially with preserved LVEF), and poor atrial contractility increasing the risk of thromboembolic complications, and atrial or ventricular arrhythmias. LCs cause diastolic dysfunction in isolated murine hearts [108], and result in direct impairment of cardiomyocyte contractility and calcium handling in adult rat ventricular cardiomyocytes [109]. Cellular abnormalities involved in LCs' cardiotoxicity include impairment of lysosomal activity and autophagy in isolated rat cardiomyocytes and in zebrafish [110, 111]. *In vitro*, the activation of a non-canonical p38α MAPK pathway has also been related to LC cardiotoxicity [112] along with mitochondria dysfunction and integrity by interacting with mitochondrial targets, such as optic atrophy 1 (OPA-1) [113]. The role of inflammation in LC-mediated toxicity and amyloidosis has been also suggested [114], while novel mechanisms of cardiotoxicity are currently under investigation [115].

Non-Hodgkin lymphoma (NHL) encompasses a heterogeneous group of hematological B-cell neoplasms with varying clinical and pathological features [116]. Diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL) are the most common subtypes. Other B cell malignancies include Hodgkin lymphoma (HL), with germinal center B lymphocytes that underwent transformation during maturation, and B cell acute lymphoblastic leukemia (ALL), an aggressive malignancy of B lymphoblasts. VTE is prevalent among B-cell hematologic malignancies [117]. The risk depends on patient-related comorbidities, immobility, previous VTE and treatment-related factors. There is an association between high-tumor burden and aggressive cancer histology [92, 118]. Stark et al. [119]. demonstrated in mice and humans that reduced blood flow velocity allows IgM to bind to the endothelium, resulting in surface exposure of P-selectin and von Willebrand factor (vWF), initiating platelet recruitment to the veins. This process is followed by platelet activation, promoting the deposition of IgG depending on fibrin and chondroitin sulfate-A but irrespectively of the antigen specificities of the IgG. This vicious circle of platelet activation leads to leukocyte recruitment and clot formation [119]. We need more data to understand the underlying pathogenetic mechanisms which contribute to an inherently prothrombotic state in clonal B-cell malignancies.

Treatment advances over the last decades have significantly improved the survival of these patients, making the impact of toxicities and comorbidities increasingly evident. The risk and prevalence of CV comorbidities and associated mortality is significantly higher in patients with NHL and HL compared to the general population [120, 121]. NHL patients have up to a 14-fold higher risk of CV mortality [122]. The risk is higher for more aggressive NHLs.

Multiagent chemotherapy HSC transplantation and mediastinal radiation [123] also induce significant cardiotoxicity.

Clonal haematopoiesis, defined as somatic mutations and mosaic chromosomal alterations in blood cells including lymphocytes, is currently investigated as a primer of CVD (reviewed in [124–126]).

Overall, B-cell hematologic malignancies are closely intertwined with CV pathology, not only through treatment-related toxicities but also via intrinsic disease mechanisms such as hyperviscosity, hypercoagulability, inflammation, and amyloid LC–mediated cardiotoxicity.

5. Immunomodulatory therapies targeting B cells and their cardiovascular effects

5.1 Cluster of Differentiation (CDs) - Cell Surface Antigens

Multiple B-cell–depleting therapies, such as monoclonal antibodies (mAb) and bispecific T-cell engagers (BiTEs), are approved for the treatment of hematologic malignancies and autoimmune diseases. These agents can influence the CV system in both beneficial and adverse ways (Fig. 2).

Rituximab (anti-CD20) is a chimeric mAb targeting the CD20 antigen on mature B lymphocytes [127], but not on stem cells or plasma cells, offering a targeted approach to modulate B-cell-driven pathology. Rituximab induces the selective temporary depletion of CD20$^+$ B cells, via antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity [128]. It has been approved for the treatment of lymphoma, rheumatoid arthritis (RA), and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, showing favorable effects during off-label use for several immune-mediated diseases such as SLE [128]. Within 48 h of rituximab infusion, adverse cardiac events such as acute HF or AMI emerge, due to cytokine release; nevertheless, long term use of the antibody is beneficial for patients with chronic myocarditis or a heart transplant [129].

In both preclinical and clinical investigations, the administration of CD20-targeted agents has shown positive impact on cardiac remodeling and HF. In specific, in a TAC myocardial hypertrophy model, Ma et al. showed that rituximab significantly enhanced heart function, reduced myocyte hypertrophy, fibrosis, and oxidative stress [130]. Similarly, in murine models of AMI, anti-CD20 antibody treatment, targeting murine CD20, improved cardiac function and decreased adverse ventricular remodeling [22]. B cell depletion can be beneficial for specific types of myocardial injury such as myocarditis. Tschope et al. observed that six patients with DCM who did not respond to initial immunosuppressive treatment, had CD20$^+$ B cell infiltration in endomyocardial biopsies and responded to rituximab infusions, with improved cardiac function [131].

Preclinical data and case reports encouraged further clinical investigations. The RITA-MI (Rituximab in Patients With ST-Elevation Myocardial Infarction) study was the first translational phase I/IIa trial to hypothesize the cardioprotective effects of anti-CD20-targeted therapies in humans. Rituximab resulted in significant B cell depletion—more than 95% within 30 minutes of infusion—with sustained and dose-dependent effects on B-cell repopulation, lasting up to six months, while it was well tolerated, with no serious side effects. The 200-mg dose demonstrated the increase of transitional B cells at 6 months, which are known to have a regulatory phenotype, while with the 1000-mg dose, the B-cell compartment was significantly depleted. Ig levels remained unaffected throughout the follow-up period [132]. Currently, the CV effects of rituximab are investigated via the RITA-MI-2 study (RITA-MI-2; https://www.clinicaltrials.gov; unique identifier: NCT05211401) aiming to determine if post–AMI B cell depletion yields measurable clinical benefits in humans [133]. In support of the above, patients with pemphigus treated with rituximab had improved long-term CV and metabolic outcomes when compared to those receiving azathioprine or mycophenolate mofetil (MMF). Rituximab treatment significantly reduced the risk for AMI, stroke, peripheral vascular disease, hypertension, hyperlipidemia, type 2 diabetes, obesity, and osteoporosis, with no increase in all-cause mortality, providing evidence for the superior CV and metabolic safety of rituximanb over conventional immunosuppressants, particularly in patients with underlying risk factors [134]. Regarding the effect of CD20-targeting in atherosclerosis progression, the hypothesis remains to be established via RITA-MI 2.

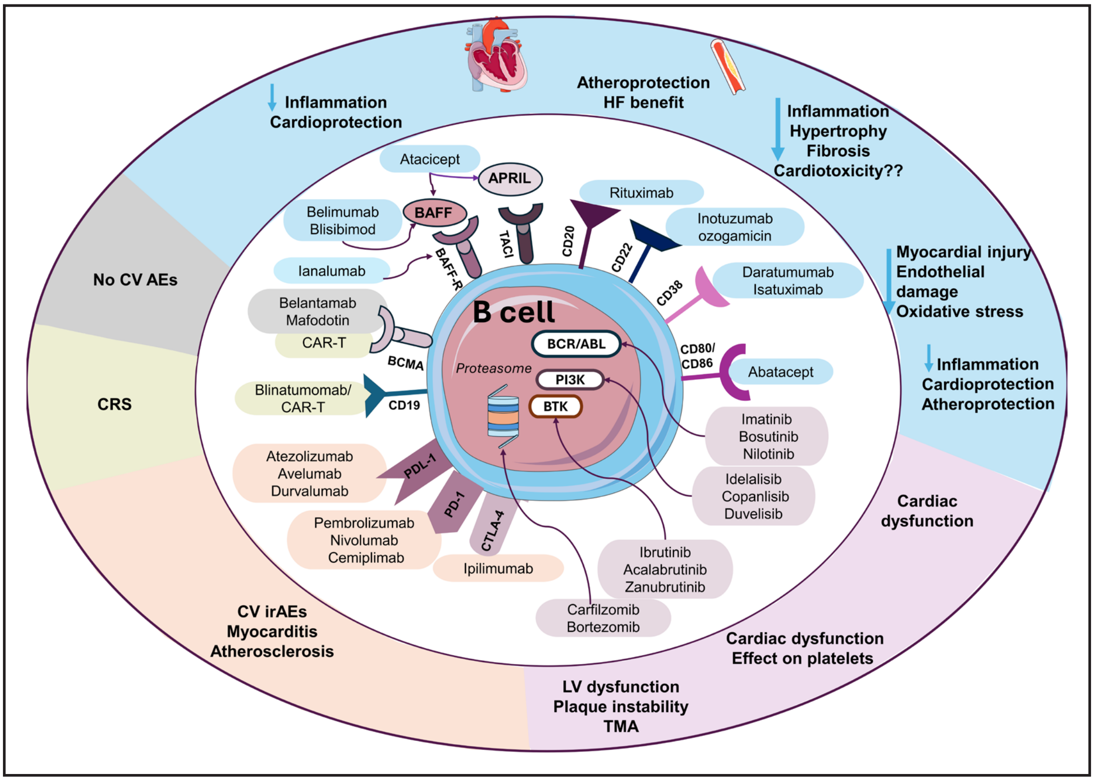

Fig. 2. B-cell–targeted therapies and their impact on the cardiovascular system. This Fig. summarizes approved B-cell–targeted therapies, their molecular targets, and their reported cardiovascular effects. These agents, developed for hematologic malignancies and autoimmune diseases, act on extracellular B-cell antigens such as CD20 (rituximab), CD22 (inotuzumab ozogamicin), CD38 (daratumumab, isatuximab), CD80/86 (abatacept), and CD19 (blinatumomab, CAR-T cells). They also target regulators of B-cell survival, including BCMA (belantamab mafodotin, CAR-T cells), BAFF (belimumab, blisibimod, atacicept), and BAFF-R (ianalumab), as well as immune checkpoints such as CTLA-4 (ipilimumab), PD-1 (pembrolizumab, nivolumab, cemiplimab), and PD-L1 (atezolizumab, avelumab, durvalumab). In addition, intracellular signaling pathways are targeted by BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib), PI3K inhibitors (idelalisib, copanlisib, duvelisib), BCR/ABL inhibitors (imatinib, bosutinib, nilotinib), and proteasome inhibitors (carfilzomib, bortezomib). By modulating B-cell function and survival, these therapies exert both beneficial and adverse cardiovascular effects, as demonstrated in preclinical and clinical studies. Beneficial effects (blue shading) include reduced inflammation, cardioprotection, and potential benefit in heart failure and atherosclerosis. In contrast, adverse effects (orange/pink shading) encompass cardiovascular irAEs, including myocarditis, atherosclerosis, cardiac dysfunction, plaque instability, TMA, and platelet dysfunction. CRS (green shading), typically observed with CAR-T therapies and BiTEs, indirectly affects the cardiovascular system, while some therapies show no clear cardiovascular adverse events, or their impact remains uncertain (grey shading). By organizing drugs according to their molecular targets and linking them to cardiovascular outcomes, the figure underscores the dual role of B-cell–targeted therapies as both potential mediators of cardioprotection and contributors to cardiotoxicity CV: Cardiovascular; CRS: Cytokine release syndrome; HF: Heart failure; AEs: Adverse events; irAEs: immune-related adverse events; LV: Left ventricular; TMA: Thrombotic microangiopathy; CD: Cluster of differentiation; BAFF(-R): B-cell activating factor (Receptor); BCMA: B-cell maturation antigen; TACI: transmembrane activator and calcium-modulator and cyclophilin ligand interactor; APRIL: proliferation-inducing ligand; PD-1: programmed cell death protein- 1; PD-L1: programmed cell death ligand- 1; CTLA-4: cytotoxic T lymphocyte-associated antigen 4; BTK: Bruton's tyrosine kinase; PI3K: Phosphatidylinositol-3-Kinase; BCR/ABL: Breakpoint cluster region/Abelson tyrosine kinase

Beyond CD20, CD38 is another B-cell differentiation antigen, which serves as both a multifunctional receptor and an ectoenzyme (extracellular enzyme). It is highly expressed on the surface of B cells, including plasmablasts and plasma cells, as well as in non-hematopoietic tissues, such as neurons, endothelial cells and cardiomyocytes [135].

In MM and AL amyloidosis, mAbs targeting CD38 exploit its overexpression on malignant plasma cells to trigger cytotoxic effects [136, 137]. CD38 has emerged as a potential therapeutic target for CVDs, due to its involvement in the pathogenesis of AMI, atherosclerosis, cardiac arrhythmias, myocardial hypertrophy and pulmonary hypertension [138]. As the primary $NAD^+/NADP^+$-degrading ectoenzyme [139], CD38 plays a crucial role in the regulation of NAD^+ homeostasis, modulating energy metabolism and calcium signaling through the CD38/cyclic adenosine diphosphate ribose/Ca^{2+} signaling pathway [135, 140]. This multifaceted role underscores potential therapeutic implications in ageing, metabolic disorders, and CVD. Supporting this, experimental studies have shown that CD38 inhibition, via miR-499a-5p-mediated downregulation in an *in vitro* model of hypoxia/reoxygenation or pharmacological agents such as thiazoloquin(az)olin(on)e 78c in an *ex vivo* model of myocardial ischemia-reperfusion (IR) injury, can reduce myocardial injury and endothelial damage following ischemia [141, 142]. Additionally, CD38 deficiency has been associated with reduced oxidative stress in the cardiac tissue from $CD38^{-/-}$ mice fed with high fat diet [143].

In clinical practice, daratumumab, a human anti-CD38 antibody, is approved as monotherapy or in combination with standard-of-care regimens for newly diagnosed or relapsed/refractory (R/R) MM and AL amyloidosis patients [144]. Multiple clinical studies have reported daratumumab's potential to exert a cardioprotective effect. In the phase III CANDOR trial, in patients receiving daratumumab on top of carfilzomib and dexamethasone, the incidence of grade ≥ 3 cardiac failure was lower [136, 145]. In the phase III ANDROMEDA trial, in patients with newly diagnosed AL amyloidosis the addition of daratumumab to bortezomib, cyclophosphamide, and dexamethasone (D-VCd) resulted in higher rates of hematologic complete response in the overall study population and across all cardiac stages [137]. Although, HF was one of the most common grade 3 or 4 adverse events, a post hoc analysis revealed, that the exposure-adjusted incidence rate for cardiac events was actually lower with D-VCd than VCd (median exposure 13.4 and 5.3 months, respectively) [137, 146]. The mechanism behind this speculated cardioprotective effect is not fully understood but could be related to the inhibition of the ectoenzymatic activity of CD38, which restores metabolic disequilibrium and calcium homeostasis in the cardiac tissue.

Isatuximab, another anti-CD38 mAb used in the treatment of MM, was initially associated with hypertension and arrhythmias, including atrial fibrillation [129, 147]. However, in a phase II trial, dyspnea was reported as the only cardiac-related event with no significant difference between patients receiving isatuximab as monotherapy or in combination with dexamethasone [148]. Similarly, in the phase III IKEMA trial isatuximab showed no significant difference in the incidence of cardiac events [149].

Inotuzumab ozogamicin, an anti-CD22 mAb, is approved for the treatment of R/R CD22-positive B-cell precursor ALL. CD22 is an inhibitory receptor expressed on B cells, and its targeting has shown immunomodulatory effects beyond oncology [150]. Specifically, in a mouse model of angiotensin II-induced nonischemic cardiomyopathy, administration of an anti-CD22 antibody attenuated cardiac hypertrophy and myocardial fibrosis, accompanied by reduced expression of pro-inflammatory cytokines such as IL-1β and TNF-α, decreased myocardial IgG deposition, and apoptosis [151]. Despite these promising preclinical findings, there are currently no clinical data supporting the CV benefit of inotuzumab in humans. On the contrary, veno-occlusive disease and QT interval prolongation, has been reported in patients receiving inotuzumab treatment [129].

Finally, abatacept, a cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) Ig, is used for the treatment of RA. It is designed to target CD80/CD86 on antigen-presenting cells, such as B cells, blocking their interactions with both the costimulatory receptor CD28 and the inhibitory receptor CTLA-4 on T cells, thereby limiting T-cell activation and immune responses [152, 153]. In B cells, this results in the promotion of Bregs functions by enhancing their ability to produce IL-10 and TGF-β [154, 155]. Abatacept reduced the CV risk when compared with a TNF inhibitor [156, 157] and decelerated atherosclerosis progression [158, 159]. Moreover, it showed cardioprotective effects in a mouse model of myocardial IR injury [160].

5.2 Receptors

B-cell maturation antigen (BCMA) is a receptor expressed on mature B cells and plasma cells, interacting with BAFF and a proliferation-inducing ligand (APRIL) [161]. Belantamab mafodotin, a BCMA-directed drug-antibody conjugate linked to the cytotoxic agent maleimidocaproyl monomethylauristatin F (mcMMAF), is approved for the treatment of R/R MM [162] and is currently under investigation in clinical trials (EMN27-NCT04617925) as a potential therapy for R/R AL amyloidosis. This antibody functions by inducing ADCC against myeloma cells. Both clinical trials and real-world data indicate a good safety profile with no CV adverse events reported [163–165].

Apart from BCMA, BAFF-R is present on the surface of mature B cells and plasma cells and has a potent selective affinity for BAFF, inducing downstream signaling pathways that lead to B-cell survival [166]. Preclinical studies propose that targeting the BAFF pathway can have a potential therapeutic benefit on CVDs, particularly AMI and atherosclerosis. In a mouse model, BAFF mAb-mediated B2-cell depletion hampered inflammation and CCL7-mediated monocyte mobilization to the ischemic heart and was associated with decreased myocardial injury and improved cardiac function post-AMI [22]. Moreover, *Ldlr*$^{-/-}$ and *Apoe*$^{-/-}$ mice with genetic or pharmacological depletion of BAFF-R exhibited a significant reduction in the B2 cell population and decreased lesion formation [167–169]. However, BAFF-targeted antibody in *Ldlr*$^{-/-}$ and *Apoe*$^{-/-}$ mice aggravated the size and complexity of atherosclerotic lesions despite depletion of B2 cells [170].

Currently, there are few drugs in use or under investigation targeting the BAFF-BAFF-R axis, mostly for hematological malignancies and auto-immune disorders. Among them, belimumab, a BAFF mAb, is the only one approved for treatment-resistant SLE [133]. In clinical practice, belimumab improves the lipid profile with an increase in HDL [171, 172] and has been associated with the enhancement of cardiac function in a patient with SLE and HFpEF [173]. Other investigational agents include blisibimod, a selective antagonist of BAFF, ianalumab, a mAb to BAFF-R, and atacicept, a transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI) recombinant fusion protein that binds both BAFF and APRIL. Thus far, no significant CV adverse events have been reported for these drugs [133].

Recently, B cells and their role in the tumor microenvironment are gaining growing attention. In this direction, various tumor-associated immune checkpoints (ICs) on the surface of B cells are identified and observed to be upregulated in the tumor [174]. These include T cell immunoglobulin and mucin domain-containing protein (TIM-1) [175], CTLA-4 [176], tumor-infiltrating T cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT) [177], programmed cell death protein-1 (PD-1)[178] and programmed cell death-ligand 1 (PD-L1) [179]. Aberrant B-cell IC signals disrupt the function of B cells per se, promoting the release of IL-10 and modulating the cellular functions of antigen-presentation, co-stimulation and memory. They also affect the tumor-killing functions of CD4^{+} T cells, CD8^{+} T cells, and Tregs, leading to tumor immune escape [174, 175].

Blocking ICs on B cells is advantageous for boosting anti-tumor immune response and suppressing tumor progression [174]. To date, antibodies targeting four ICs, namely CTLA-4 (ipilimumab), PD-1 (pembrolizumab, nivolumab, cemiplimab), PD-L1 (atezolizumab, avelumab, durvalumab), and lymphocyte activation gene 3 (LAG-3) (relatlimab), have been approved for the treatment of several malignancies, such as melanoma, non-small cell lung cancer, classical HL, either as monotherapy or as adjuvant therapy [180].

Clinically, immune checkpoint inhibitors (ICIs) have been associated with immune-related adverse events (irAEs), which encompass rare but severe CV complications, such as myocarditis, cardiomyopathy, pericardial disease, arrhythmias, and atherosclerosis [181].

Underlying cardiotoxicity mechanisms have been proposed, including increased systemic activation of T cells and release of pro-inflammatory cytokines [182] and especially IL-17A [183], endothelial activation and microvascular coronary endothelial dysfunction [184, 185] and cross-reactivity between tumor-infiltrating T cells and common antigens in cardiac and endothelial cells [186]. However, only scarce data exist about the role of B cells. A few studies have described possible mechanisms of B cell-mediated toxicity, either through the activation and expansion of B autoreactive populations due to activation of autoreactive clones by ICIs, recognition of neoantigens homologous to non-cancer antigens, or modified cytokine expression profiles [187]. Interestingly, increased activation of B cell and plasmablast levels as well as the presence of autoreactive antibodies have been observed in ICI-treated patients at increased risk of irAEs [187, 188].

5.3 Interaction with other cells

Chimeric Antigen Receptor T-cell (CAR-T) and BiTE therapies have transformed the treatment landscape for hematological malignancies such as ALL, B-cell lymphomas and MM. CV toxicities have emerged as an increasingly recognized cause of treatment-related morbidity and mortality [189].

CAR-T cells are *ex vivo* genetically engineered T cells programmed to induce a cytotoxic immune response after the recognition of specific tumor-associated antigens, such as CD19 in B-cell malignancies (tisagenlecleucel and axicabtagene ciloleucel) or BCMA in MM [144, 189]. Clinical trials of CAR-T cell therapy have reported a low incidence of cardiotoxicity, possibly due to patient enrollment criteria. However, subsequent retrospective cohort studies highlighted the occurrence of major adverse CV events (MACE) in 10-20% of patients [189]. These include tachyarrhythmia, hypotension, troponin elevation, cardiomyopathy, pericardial and pleural disorders, VTE and cardiogenic shock [190–192].

The exact mechanisms of T-cell therapy–induced cardiotoxicity remain elusive. The predominant mechanism involves indirect cardiotoxic effects following immune system activation: tumor-directed inflammation within the microenvironment can lead to a systemic cytokine storm, known as cytokine release syndrome (CRS), that impairs cardiac function [193–195]. CRS is characterized by increased levels of pro-inflammatory cytokines, primarily IL-6, IL-1, TNF-α, and nitric oxide, released by activated T cells, macrophages and monocytes [196]. IL-6 has been proposed to activate the gp130/STAT3 signaling pathway and induce oxidative stress. Subsequently, this leads to mitochondrial dysfunction, cardiomyocyte apoptosis and cardiac hypertrophy. In addition, IL-6 modifies calcium handling and impairs myocardial contractility [197]. CRS treatment involves the administration of tocilizumab, (an antibody binding and blocking the soluble and transmembrane IL-6 receptor), particularly in severe cases, to decrease the risk of cardiotoxicity [189]. Additional proposed mechanisms for CAR-T cell–associated cardiotoxicity include the direct T cell-mediated damage to cardiac tissue due to cross-reactivity with cardiac antigens via molecular mimicry or immune alloreactivity. Moreover, T cells can inadvertently recognize and attack heart-specific proteins unrelated to the tumor, leading to off-target cardiac toxicity [189].

BiTEs are fusion proteins with 2 different antigen-binding sites: one directed against the CD3 molecule, which leads to downstream activation of cytotoxic T lymphocytes, and another directed specifically at an antigen present on malignant cells [198]. Blinatumomab, a bispecific CD19/CD3 antibody targeting CD19 on B cells, has been approved for R/R CD19-positive B-cell precursor ALL [199]. Data regarding the incidence of cardiotoxicity are limited, but in clinical practice, it has been associated with CRS, tachycardia and HF [189].

5.4 Intracellular targets on B cells

PIs form the cornerstone of combination regimens for patients with MM and AL amyloidosis, although they are also used for treating other malignancies. PIs target the chymotrypsin-activity of the 20S unit of the proteasome [200], causing proteome instability due to the accumulation of aggregated, unfolded, and/or damaged polypeptides; this sustained proteome instability induces cell death.

Disruption of proteasome function has been associated with the development of CVD [201]. Accumulation of misfolded proteins has been observed in various cardiomyopathies, including hypertrophic, dilated, and desmin-related forms [202], and significant impairment of proteasomal activity has been documented in HF and in myocardial tissue obtained from patients with hypertrophic cardiomyopathy [203]. Therefore, pharmacological inhibition of the proteasome can be particularly harmful in cases with pre-existing cardiac dysfunction or advanced age.

Carfilzomib, an intravenous irreversible PI, is associated with increased incidence of hypertension (9-27%) [204, 205], HFrEF (4.1-16.2%) [204, 206], ischemic heart disease (1.8-17.6%), and arrhythmias (2.4-7%) [206, 207]. Bortezomib, an intravenous reversible PI, is also associated with CV toxicity, albeit at a lower degree compared to carfilzomib [147, 200]. The only orally administered PI ixazomib is generally not associated with a high risk for CV toxicity, apart from scarce evidence [200].

Bortezomib’s cardiotoxicity is associated with impaired cardiomyocyte survival and contractility due to protein accumulation, mitochondrial dysfunction and worsening of the atherosclerotic plaque vulnerability [144, 208]. The higher risk of CV toxicity of carfilzomib is likely linked to irreversible inhibition of the proteasome’s proteolytic activity and the broader dosing spectrum [200]. The potential underlying mechanism of cardiotoxicity and LV dysfunction involves mitochondrial dysfunction [209]. In a cell model using human induced pluripotent stem cell-derived cardiomyocytes, carfilzomib reduced mitochondrial membrane potential, ATP production, and mitochondrial oxidative respiration, resulting in decreased cardiomyocyte contractility. Carfilzomib treatment also downregulated gene expression of extracellular matrices, the integrin complex, and cardiac contraction [144, 210]. Impaired autophagic signaling was observed with carfilzomib in *in vivo* models of young and aged mice [211, 212]. Additionally, data indicate a possible role of the pyruvate oxidation pathway in mitochondrial dysfunction, as evidenced by the down-regulation of pyruvate and up-regulation of lactate dehydrogenase B among patients who experienced CV adverse events with carfilzomib [213]. Carfilzomib, like bortezomib, affects vascular smooth muscle cells, probably exacerbating the vulnerability of atherosclerotic plaques in patients [136].

Another important vascular complication observed with all proteasome inhibitors is thrombotic microangiopathy (TMA) [200, 214]. Proteasome inhibition can disrupt protein homeostasis within vascular cell walls, promoting cellular aging, cell cycle arrest, and programmed cell death [201]. Increasing *in vitro* evidence supports that the ubiquitin-proteasome pathway (UPP) regulates several endothelial cell functions, including the expression and activation of endothelial nitric oxide synthase (eNOS), and the balance of vasodilatory and vasoconstrictive signaling [215]. Additionally, the UPP contributes to vascular inflammation by modulating NF-κB activity and upregulating adhesion molecule expression [216]. While the full pathophysiologic mechanisms are not completely understood, microvascular injury appears to be linked, in part, to the suppression of vascular endothelial growth factor (VEGF) signaling [200].

Paradoxically, under certain experimental conditions, short-term proteasome inhibition has shown cardioprotective effects, particularly by attenuating or preventing left ventricular hypertrophy in animal models of chronic pressure overload and in hypertensive Dahl salt-sensitive rats [217]. Moreover, treatment with proteasome inhibitors at low doses enhanced endothelial-dependent vasodilation in rat aortic rings *in vitro*, via increasing the expression and activity of eNOS and reducing the levels of endothelin-1 [215, 218, 219].

Moreover, intracellular signal transduction downstream BCR, mediated by tyrosine kinases, mainly Bruton’s tyrosine kinase (BTK) and PI3K, influences B-cell activation, proliferation and differentiation [220, 221]. Lately, BTK inhibitors and PI3K isoform-specific inhibitors have been approved for the treatment of hematologic malignancies.

Specifically, ibrutinib, an irreversible BTK inhibitor, has received approval for the treatment of CLL, MCL, and Waldenström’s macroglobulinemia. In the clinical setting, the drug is reported to induce cardiotoxicity, mainly arrhythmias and hypertension [220], possibly due to interactions with PI3K and other TEC pathways in cardiomyocytes [144, 222]. In platelets, BTK inhibition is associated with central nervous system bleeding or ischemia, because it affects platelets' activation [223, 224]. Recent evidence indicates that newer BTK inhibitors, such as acalabrutinib and zanubrutinib, have increased selectivity for BTK, resulting in reduced cardiac implications [225, 226].

To date, three PI3K inhibitors have been approved for the treatment of CLL and indolent NHL: idelalisib, copanlisib and duvelisib [221], but CV adverse events can occur, including arrhythmias and cardiac dysfunction due to the regulatory role of specific PI3K isoforms in the heart [129, 227].

Finally, breakpoint cluster region (BCR)-Abelson (ABL) tyrosine kinase, is implicated in signal transduction pathways that regulate survival and proliferation in hematopoietic cells. It is used for the treatment of CLL in combination with other agents, such as imatinib, bosutinib and nilotinib [228, 229]. Inhibitors of BCR/ABL cause various forms of cardiotoxicity, such as congestive HF, AMI, coronary and peripheral artery disease, peripheral arterial occlusive disease, VTEs, and arrhythmias [129, 230]. The mechanism underlying these effects is not fully understood, but it appears to involve mitochondrial dysfunction [129, 231], autophagy and cardiomyocyte apoptosis [232, 233].

Taken together, B-cell–targeted immunomodulatory therapies have revolutionized the treatment of hematologic malignancies and autoimmune diseases, being increasingly recognized for their CV effects. Anti-CD20 therapy (rituximab) has demonstrated potential cardioprotective effects by attenuating adverse remodeling in preclinical models and is under investigation in post-AMI settings in humans. CD38-targeting antibodies, such as daratumumab and isatuximab, can restore metabolic disequilibrium and calcium signaling by regulating NAD^+ homeostasis, though further mechanistic studies are needed. Other agents, including inotuzumab (anti-CD22) and abatacept (CTLA-4-Ig), show promising preclinical cardioprotective effects. On the contrary, ICIs can induce rare but severe immune-related CV toxicities, including myocarditis. Cellular therapies (CAR-T, BiTEs) carry risk for CRS–mediated cardiotoxicity, underscoring the need for careful monitoring. Intracellular B-cell signaling inhibitors (BTK, PI3K, BCR-ABL inhibitors) and PIs are associated with arrhythmias, hypertension, HF, and vascular complications, possibly due to mitochondrial and endothelial dysfunction and impaired autophagy. Collectively, these therapies highlight the dual potential for CV harm and benefit, underscoring that targeting specific surface markers is more beneficial for the CV system than tackling intracellular pathways in B cells.

6. Conclusions

Despite decades of research, the multifaceted role of B cells —as antigen-presenting cells, cytokine producers, and antibody-secreting effectors— remains underrecognized as a driver of disease and a therapeutic target in CV pathology. Therapeutic interventions targeting intracellular signaling pathways in B cells are frequently associated with cardiotoxicity and CV adverse events. This is largely due to the shared signaling mechanisms —such as proteasome function and PI3K signaling— between B cells and cell types of the myocardium including cardiomyocytes and endothelial cells. Consequently, using such broad-spectrum immunomodulators such as PIs are likely unsuitable as therapeutic agents in CVD. Emerging therapies targeting intracellular pathways in B cells must be rigorously monitored in early clinical trials for CV adverse events.

In a translational perspective, testing B cell-related therapeutics for CVD with antibodies to target specific cell surface markers would be more rational. Targeting cell surface markers that are expressed by B cells such as CD20, CD38, or CD80, and modulating the BAFF pathway, represent promising therapeutic approaches, though repurposing existing agents for AMI or HF requires optimized, tailored dosing regimens. Future directions could involve the development of small molecule inhibitors of CD's and BCMA or RNA silencing therapies to exploit B cell depletion and long-term cardioprotection, and to avoid the short-term antibody-related cardiotoxicity and CRS. Yet, the efficacy of these strategies is doubtful in hematologic malignancies.

Receptor specificity must be carefully balanced to preserve the protective functions of specific subsets such as B1 cells and Bregs [234] especially in the heart and avoid compromising overall immune competence. The broader concept of immunomodulation through metabolic reprogramming could serve as an alternative to modify HF outcomes [235–237]. More comprehensive studies are needed to better understand the contribution of each B cell subset in cardiac disease and hematologic malignancies, having as ultimate goal to optimize B cell-targeted therapies. In this context, a precision medicine approach should be adopted, integrating both disease characteristics and patient-specific immune profiles—particularly B-cell subset composition—into clinical decision-making. Standardized assays for circulating B-cell subtypes and antibody signatures should be validated in large, multicenter cohorts and incorporated into risk prediction models to enable early CVD risk stratification, therapeutic guidance, and monitoring of treatment response.

Abbreviations

AL (Light chain-Amyloidosis); ALL (Acute lymphoblastic leukemia); ADCC (‚Antibody-dependent cell-mediated cytotoxicity); AMI (Acute myocardial infarction); APRIL (Proliferation-inducing ligand); ARVC (Arrhythmogenic right ventricular cardiomyopathy); BAFF(-R) B-cell (activating factor (Receptor)); BiTEs (Bispecific T-cell engagers); BCMA (B-cell maturation antigen); BCR (B cell receptor); BCR/ABL (Breakpoint cluster region/Abelson tyrosine kinase); Bregs (B regulatory cells); BTK (Bruton's tyrosine kinase); CAR-T (Chimeric Antigen Receptor T-cell); CCL (C-C chemokine ligand); CCR (C-C chemokine receptor); CD (Cluster of differentiation); CLL (Chronic lymphocytic leukemia); CLP (‚Common lymphoid progenitors); CMP (‚Common myeloid progenitors); CRS (Cytokine release syndrome); CSF1 (Macrophage colony-stimulating factor); CTLA-4 (Cytotoxic T lymphocyte-associated antigen 4); CV (Cardiovascular); CVD (Cardiovascular disease); CXCL (‚CXC chemokine ligand); CXCR (CXC chemokine receptor); DCs (Dendritic cells); DCM (Dilated cardiomyopathy); DLBCL (Diffuse large B-cell lymphoma); D-VCd (Daratumumab, bortezomib, cyclophosphamide, and dexamethasone); eNOS (‚Endothelial nitric oxide synthase); HC (Heavy chain); HL (Hodgkin lymphoma); FcγRs (Fc gamma receptors); (FL‚Follicular lymphoma); HF (Heart failure); HFpEF (Heart failure with preserved ejection fraction); HFrEF (Heart failure with reduced ejection fraction); HSCs (‚Hematopoietic Stem Cells); ICs (Immune checkpoints); ICIs (Immune checkpoint inhibitors); IFN-γ (Interferon gamma); Ig (Immunoglobulin); IgAP (Immunoglobulin-associated proteome); IL (Interleukin); IMiDs (Immunomodulatory drugs); IR (Ischemia-reperfusion); IRA (Innate response activator); irAEs (Immune-related adverse events); Kd (Carfilzomib and dexamethasone); KdD (Daratumumab, carfilzomib, and dexamethasone); LAG-3 (Lymphocyte-activation gene 3); LC (Light chain); LPS (Lipopolysaccharide); LVEF (‚Left ventricular ejection fraction); GM-CSF (Granulocyte-macrophage colony-stimulating factor); mAb (Monoclonal antibodies); MACE (Major adverse cardiovascular events); mcMMAF (Maleimidocaproyl monomethylauristatin F); MZ (Marginal Zone); MG (Monoclonal gammopathy); MGTS (Monoclonal gammopathy of thrombotic significance); MGUS (Monoclonal gammopathy of undetermined significance); MHC (Major histocompatibility complex); MM (Multiple myeloma); MMF (Mycophenolate mofetil); NHE1 (Sodium-hydrogen exchanger-1); NFATC2 (Nuclear factor of activated T cells, cytoplasmic differentiation 2); NHL (Non-Hodgkin lymphoma); OxLDL (Oxidized low-density lipoprotein); PBMCs (Peripheral blood mononuclear cells); PD-1 (Programmed cell death protein-1); PD-L1 (Programmed cell death- ligand 1); PIs (Proteasome inhibitors); RA (Rheumatoid arthritis); R/R (Relapsed/Refractory); SDF1 (Stromal cell-derived factor 1); SGLT-2 (Sodium-glucose co-transporter-2); SLE (Systemic lupus erythematosus); TAC (Transverse aortic constriction); TACI (Transmembrane activator and calcium-modulator and cyclophilin ligand interactor); TGF (Transforming growth factor); TIGIT (Tumor-infiltrating T cell immunoreceptor with immunoglobulin and ITIM domain); TIM-1 (‚T cell immunoglobulin and mucin domain-containing protein); TLRs (Toll-like receptors); TMA (Thrombotic microangiopathy); TNF-α (Tumor necrosis factor alpha); Tregs (T regulatory cells); UPP (Ubiquitin-proteasome pathway); VEGF (Vascular endothelial growth factor); VTE (Venous thromboembolism); WM (Waldenström's macroglobulinemia);

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