ISSN: 2832-7708

Review Article

Insights of Cardiovascular Pharmacology Research

# G-Protein-Coupled an Emerging Therapeutic Target in Cardiovascular Diseases

**Ullah Kifayat* and Liu bin**

*Jilin University Norman Bethune Health Science Center*

***Corresponding Author**
Ullah Kifayat, Jilin University Norman Bethune Health Science Center.

**Submitted:** 2023, Oct 10; **Accepted:** 2023, Oct 29; **Published:** 2024, Jan 04

**Citation:** Kifayat, U. Bin, L. (2024). G-Protein-Coupled an Emerging Therapeutic Target in Cardiovascular Diseases. *Insig Cardio Vasc Phar Res, 4*(1), 01-16.

**Abstract**

*G-protein-coupled receptors GPCRs (guanine nucleotide binding protein) approximations varies in regards of numbers, are 7-seven transmembrane spanning (7 TM receptors) helices. Being a diverse membranous surface receptor, said receptors are mainly responsible in regulations of physiological as well as pathophysiological cardiac function. Henceforth, they are target for course of action of hypertension and heart failure drugs and it represents one of largest group of surface receptors in body. There are numerous GPRC's antagonist such as β-adrenergic receptors (βARs), Angiotensin-II receptors (Ang-II), endothelin and adenosine receptors. In cardiovascular diseases such as hypertension (HTN), Heart Failure (HF) and coronary artery diseases (CAD) these drugs are now standard care of therapy in daily practice. GPCRs activation and downstream signaling subsequently, in latest discovery have shown new mechanism of actions were thought to be acknowledged in late 80's and 90's. Yet, recent studies shown that currently there are small fraction of cardiac GPCR repertoire are targeted by available therapeutic drugs. Nevertheless, it indicates that there is a lot to explore in unacknowledged aspects in heart GPCRs. In this review I will try to update and reviews those aspects studied by the respective experts and Those GPRCs which influences cardiovascular system. My review will provide insight into β-arrestine/effectors complexes which has shown distinctive influence over cardiac physiology and disease. This review focus on both expansion of repertoire GPRCs, β-arrestine and its effect on subsequent signaling pathways. This review deliberates the progressing in the field of GPRCs signaling, ligand bias, and β-arrestine mediated signaling.*

**Keywords:** Gpcr, β-Arrestine, Bias, Heart Failure, Hypertension, Coronary Artery Disease, Cardiovascular System

## 1. Introduction

Heart failure is a clinical condition in which there is mark reduction in pumping capability of myocardium to meet the body demand. Prevalence of Heart failure results in high morbidity and mortality. Annually it affects nearly 6.5 million adults in America, global estimation is 26 million and cost 30 billion USD in expenditures in healthcare. Hospitalization due to heart failure reaches 20-40% in between 1 to 5 years of mortality rate [1]. Therefore, knowing the mechanism of fundamental progress of heart failure is a vital to reduced mortality and morbidity due to HF [1]. Most common causes which lead to Heart failure is Chronic Hypertension, Coronary artery diseases such as myocardial infarction, cardiomyopathies course, vulvar heart diseases, or viral myocarditis. Reduced blood ejection and ventricular filling occurred as result of these stimuli [2]. According to perception of Cardiac function HF are illustrated by HF with preserved ejection function (HFpF), also known as diastolic HF with normal myocardium contractility but reduction ventricular filling, and HF without preserving myocardium contractility with reduction in ejection fraction which is also known as systolic HF [3]. In both these types of HF results in structural and functional deformities primarily prompted cell width, length, or both which causes enlargement of cardiac myocytes mainly of LV termed as hypertrophy. There are diverse intrinsic and extrinsic stimuli which can initiate cardiac myocytes hypertrophy such stress, hormones, cytokines, growth factors have their influence on wide-ranging of GPCRs cell membrane receptors. Amongst the cell surface receptors GPCRs (Guanine nucleotide binding protein) represents the largest and versatile group of surface receptors with wide range of signal transduction in convening signal from extracellular to intracellular consist of 7–transmembrane (7TMRs) GPCRs has vital role in regulatory of physiological process of myocardium for endogenous ligands such as Angiotensin-II and norepinephrine activate chronically their receptors angiotensin-II type-I (AT1Rs) and β-Adrenergic ( βARs) respectively [4, 5]. As increase in demand of perfusion subsequently increase of workload on myocardium increased as well which cause defective remodeling of heart and myocardium death. These receptors are blocking from activation by Ang-II receptors' blockers, Beta-Blockers, Angiotensin converting enzyme (ARBs) inhibitors extensively used therapeutic drugs against HF [6]. My review will highlight and provide insight GPCRs signaling and its physiological role, implication when bearing in mind HF in cardiac myocytes.

### 1.1. Gpcr Signaling (G-Protein Mediated)

In traditional pattern G-protein is mainly responsible for the transduction of signal from extracellular to intracellular by binding with the nucleotides GTP and GDP hence because of this capability named G-protein. Signaling transduction inside the cell occurs by binding GTP to G-protein (activated or on) while binding of GDP to G-protein causes (Inactivation or off) of the receptor like molecular switch for signaling transduction. Heterotrimeric G-proteins are consisting of three subunits namely α, β, and γ [7]. When ligand binds with GPCR externally goes under conformational changes (stabilizes) upon receiving signal, causing G-protein to exchange GDP for GTP which leads to its activation on GPCR α subunit. Upon activation the Heterotrimeric G-protein splits into two units, the Gα subunit bounded by GTP and Gβγ dimeric complex. Both the subunit has wide range of signaling effectors to be bound to such as ion channels and enzymes which subsequently give rise to second messenger. Hydrolyzation of GTP to GDP and unbound by Gα catalytic subunit will cause to reunite it with dissociated Gβγ. Thus, activation cycle of G-protein ends illustrated below [8]. (Figure-1) At present there are total 21-Gα subunits, 6-Gβ subunits and 12Gγ subunits. Gα catalytic subunit of Heterotrimeric G-protein are usually meant in a Heterotrimeric G-protein and on bais of that is divided into four-4 types namely $G\alpha_s$ (Gα-stimulatory), $G\alpha_i$ (Gα-Inhibitory), $G\alpha_q$, $G\alpha_{12/13}$. These multiplicity in families of G-protein subunits has wide range of function in signal transduction such as $G\alpha_s$ stimulate adenylyl cyclase an effector enzyme subsequent cAMP second messenger production which causes protein kinase A (PKA) activation and mediate several cellular responses by means of intracellular proteins phosphorylation [8]. In comparison adenylyl cyclase is inhibited by the action of Gαi (Gα-Inhibitory) $_{which}$ results in cAMP diminishing intracellulary. Phospholipase C (PLC) is activated by the action of Gαq which in turn cleaved phosphatidylinositol 4-5 phosphate a membrane bounded into inositol 1, 4, 5-tri-phosphate and diacylglycerol second messenger then causes indorses $Ca^{2+}$ from endoplasmic reticulum [9]. Cellular signaling is stimulated by protein kinase C (PKC). Protein kinase C is activated by diffusion of diacylglycerol and increased in intracellular $Ca^{2+}$. Small GTPase are activated by the $G\alpha_{12/1}3$ G-protein [10, 11]. Besides its activity on cell surface receptors, GPCRs has diverse locality can mediate downstream signal activation in additional section of the cell such as G-protein Gαs activity endorses Cyclic AMP production in early endosomes upon activated by $\beta_2$-adrenergic receptor($\beta_2$AR) [12]. Adenylyl cyclase is activated by the action of β-adrenergic receptor ($\beta_1$AR) nuclear membrane of cardiac myocytes [13]. Nuclear $Ca^{2+}$ concentration is regulated by nuclear Endothelin receptors (ET) upon stimulated [14]. Extracellular signal mediated kinase located in plasma membrane of caveolae activated by αI-adrenergic receptors (αIAR) of nucleus and signaling is inside-out [15, 16].

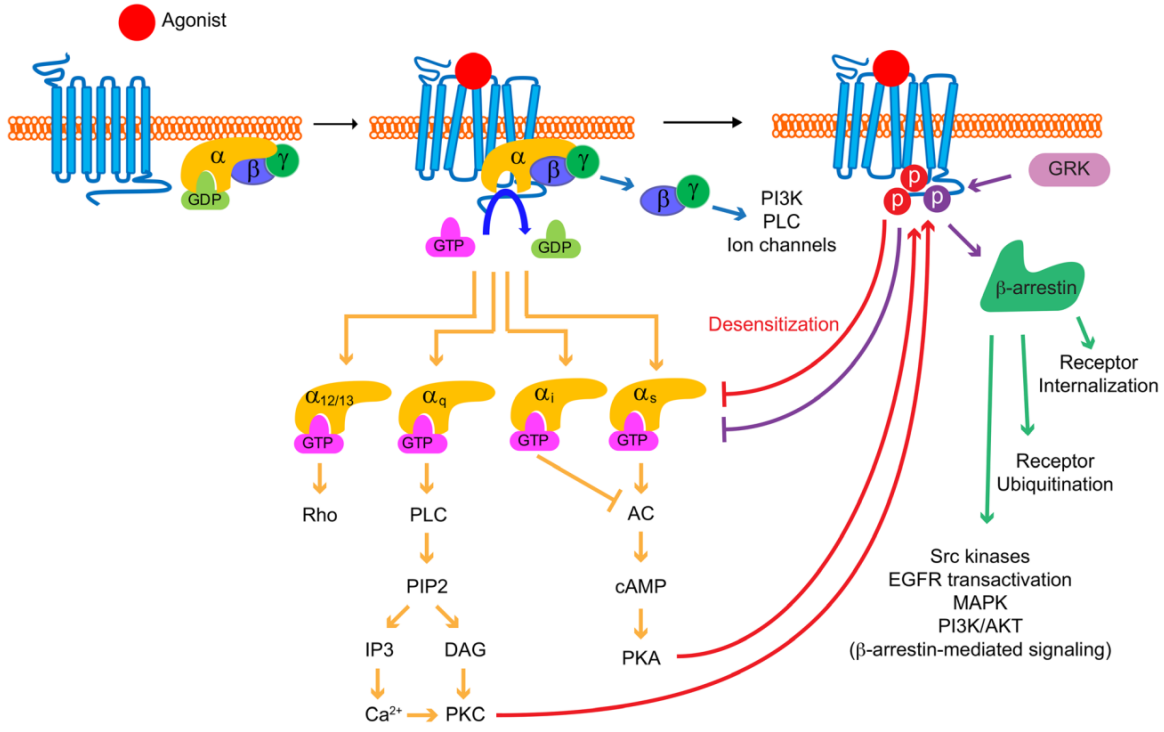


**Figure 1:** G-protein-coupled receptors signaling Schematics.

Upon binding of agonist ligand causes the triggered a chain of command G-protein goes under conformational changes, At Gα catalytic subunit GDP is exchange for GTP which will results in separation of Gα subunit from Gβγ dimeric, upon receiving signal from ligand will cause activation downstream. Protein kinase-C (PKC) and Protein kinase-A (PKA) phosphorylates the receptors upon activated by G-protein which causes the switch off G-protein signaling marked by red lines in above Figure-1 (Heterologous desensitization and phosphate). B-arrestine recruitment occurred when phosphorylation of GPCR is mediated by GPCR kinase (GRK) over and done with Sterically forbidding resulting in desensitization colored purple

line in above Figure-1 (Homologous desensitization, Phosphate) followed by receptor ubiquitination and receptor internalization. β-arrestine mediated signaling gets activated upon rendezvous of β-arresting to its receptors.AC denotes Adenylate cyclase; AKT denotes serine/threonine kinase or also referred to as Protein kinase; DAG, diacylglycerol; EGFR, Epidermal growth factor receptor; IP3: inositol 1, 4, 5 triphosphates; MAPK, Mitogen activated protein kinase; PI3K, Phosphoinositide 3-kinase; PIP2, phosphatidylinositol 4, 5-biphosphate; and last one PLC, phospholipase.

### 1.2. Gpcr Desensitization

GPCR signaling pathway is necessary to maintain function of cell. Persistent signaling can affect cellular function and can results in unwanted outcomes such heart failure. Therefore, GPCR signaling pathway termination should tightly regulated [17, 18]. In deactivation of G-protein signaling pathway there are numerous ways to terminate the signaling like one mention above along with that there is desensitization of G-protein receptors phosphorylation by either heterologous or homologous desensitization. Heterologous desensitization occurs when remnant of threonine and serine on third intracellular loop (3rd-ICL) while homologous desensitization involves C-terminus (carboxyl terminal tail). In Heterologous desensitization terminate the signaling, by PKA and PKC kinases second messenger signaling receptor activated phosphorylate the remnant of amino in their prime location intracellular loop (ICL) and C-terminus to split G-protein from their associated. Phosphorylation mediated by PKA can altered receptor coupler to any subtype of G-proteins [19]. For case in point phosphorylation of β2AR mediated by PKA also negatively affects the affinity of Gαs while at the same time enhanced the affinity of Gαi hence halts Gαs activated production of cyclic AMP and initiate signaling pathway mediated by Gαi. Moreover, halting the production of cAMP, cardiac myocytes βARs phosphorylation intermediated by PKC and PKA kinases prompts conscripting β-arrestine and phosphodiesterase-4(PDE-4) which stimulates cAMP degradation. In protracted mediation of βAR PDE-4 vital enzyme in maintaining equipoise between degradation and Cyclic AMP production in desensitization over and done with hydrolyzing cyclic adenosine monophosphate,(Figure-2) βAR phosphorylation mediated by PKA are boosted and switching from Gαs to Gαi homologous desensitization of GPCR is another way of terminating signaling pathways through carried out by a family of enzymes (GR Kinases) which phosphorylate the receptors in the presences of these enzymes (GPCR Kinases) [19-21]. There are total seven-7 GRK located in different tissues of the body [22]. GRK1 and GRK7 are specifically located in Retinas of the eyes, GRK4 is located in the Germinal cells expressed in spermatozoa, while remaining four members of the GRK, 2, 3, 5, 6, omnipresent in body tissues [22]. GRKs predominantly responsible for the mediation of threonine and serine remnants phosphorylation which enhances beta-arrestine translocation to its respective receptor by GPCRs activating ligand specifically in C-terminus. Moreover, ephemeral activation of Beta-arrestine can be done by transmembrane core GPCR other than the formation of GPCR beta-arrestine phosphorylation of tail o receptor. Internalized receptor activation enhances while beta-arrestine proscription of G-protein coupling sterically [23]. Direct Collaboration between beta arrestine the aforementioned Clathrin and Clathrin adaptor protein-2 (AP-2) marked the coated pits of Clathrin which results in receptor internalization [24]. There is slow and fast recycling of internalization receptors to plasma membrane or gets degraded by the action of lysosomal enzymes in early stage of endosomes or late endosomes in protracted internalization respectively [25]. Downstream signaling pathways are continuously activated by internalization of GPCRs are said to be persisted in membrane bounded vesicle (endosomes) revealed by current studies [10]. Beta-arrestine has wide range of regulation and degradation of signaling transduction of receptors internalization by ubiquitylation [13, 26]. And target for these is control by ubiquitin and de-ubiquitinase thereby tightly regulate ubiquitination and de-ubiquitination phenomenon [27].

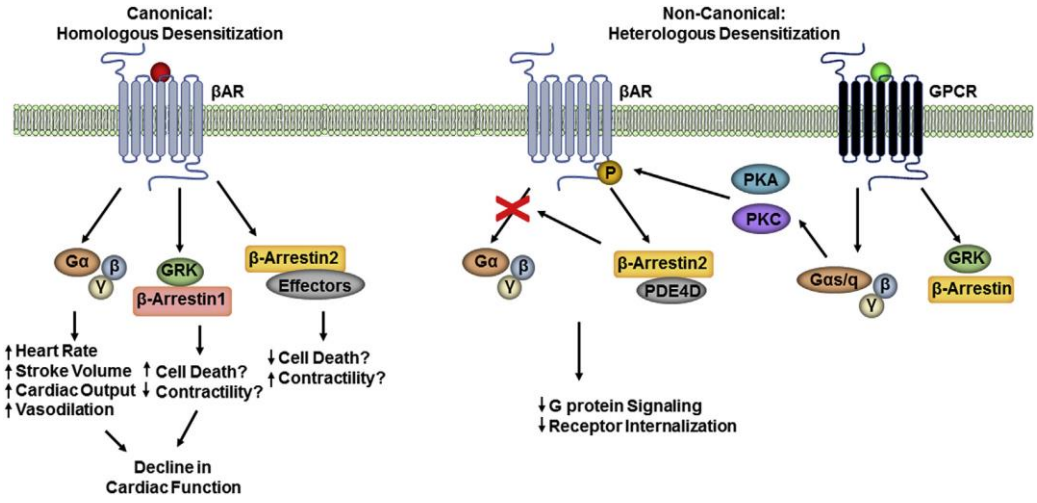


**Figure 2:** Cardiac myocytes GPCR signaling mediated by Beta-arrestine over and done with Heterologous and Homologous Desensitization. This figure shows the selective mediation of Beta-arrestine (Beta-arrestine 1, 2) in course of desensitization through heterologous (non-canonical) and homologous (canonical) GPCRs and their influence over cardiac myocytes downstream signaling. Gα- Alpha subunit; Gαs, alpha subunit stimulatory; Protein kinase-A (PKA); Protein kinase-C (PKC)

### 1.3. β-Arrestine-Mediation: Gpcr Signaling and Biased Agonism

Beta-arrestine are member of Arrestine 1 to 4, arrestin1 and arrestine4 are widely manifested in retinas of the eyes and arrestin2 also known as arrestine1, arrestine3 referred to as arrestin2 are extensively spread other tissue and expressed [28]. These four Arrestine proteins have similar homology in their structure and high sequence made up of N, C terminus which constructed on anti-parallel beta-strands, intervening loops [29, 30]. Even though well define structure of the two isoform arrestine has the capability to engage wide range of GPCRs activation by the agonist. GPCR signaling are critically mediated by the beta-arrestine in either activation of the receptors internalization and desensitization of the signaling as well [28]. Signal transduction across membrane downstream signaling pathway intracellular function is achieved through the action of scaffold/ adaptor protein, Such as the initiating activation of ERK by the complex formation receptor-Src. Receptor-Src are formed when tyrosine kinase (c-Src) and bet-arrestine interact directly. Beside that β1-AR and AT1Rs can regulate the activation across the membrane of epidermal growth factor receptor (EGFR) which can also activate the ERK [31]. ERK activation is mediated by Beta-arrestine which in turn regulates the function of MAPK-1 (mitogen activated Protein kinase) and relating Threonine/ Serine kinase-1 (MNK1) in synthesis of protein, along with that beta-arrestine regulates BCL-2 concomitant agonist cell death (BAD) phosphorylation meddling anti-apoptotic signals [32-34]. Action of mediated by G-proteins are quick and momentary whereas beta-arrestine mediated process are unhurried and brief in duration [35]. For instance, activation of ERK by G-protein enter nucleus and can cause desired transcription by phosphorylation while beta-arrestine mediated remains in cytoplasm matrix, causes regulate diverse cellular responses and substratum. Despite being thought of Beta-arrestine1 and beta-arrestine2 functionally an obsolete but recent studies have shown that beta-arrestine1 versus beta-arrestine2 has influence on cardiac myocytes function and survival, As it desensitizes Beta1-adrenergic receptors, Beta-arrestine one may be considered to have negative impact on cardiac myocardium while advances pro inflammatory substances and apoptotic activity signaling, beta-arrestine inhibition of signaling which lead to cell death [36, 37]. Latest data has shown both in vivo and in vitro that Beta-arrestine2 may enhanced myocardial contractility acting directly on Sarco(endo)plasmic reticulum Ca2+ ATPase (SERCA2a) boost its performance prompting SUMOylation, effected stimulated due to signal transduction of beta1-arrestine receptor [39]. In addition to that induced myocardial infarction in a model mouse with cardiac dysfunction was created for study purposes, in model mice with beta-arrestine2 overexpression has shown to have enhanced SUMOylation of Sarco(endo)plasmic reticulum Ca2+ ATPase and vastly increase myocardial function moreover a significant reduction in adversative events post MI such cardiac remodeling over and done with fibrosis and apoptosis [38]. While these studies may show that Beta-arrestine may be a potential treatment in Heart failure, but another study oppose that stating in the course of acute myocardial injury an overexpression of Beta-arrestine2 may have negative effects [38]. Furthermore, in this study cardiac myocytes were cultured and specifically unregulated for the expression Beta-arrestine2 greater instigated ischemic reperfusion injury, increased myocardial cell death were noted in induced myocardial ischemic injury mice models, however on other hand insufficiency of functionality or knock down of beta-arrestine2 may have conveyed negative effect on reperfusion in myocardial ischemic injury. The Deteriorating of phenotype happened when beta-arrestine2 and Phosphoinositide 3 kinase (PI3K) subunit the p85 interacted that regulates the complex formed by p85-PI3K/Cav3, ensuing activation of glycogen synthase kinase and Akt occurs once PI3K mediation is blocked [39]. Conflicts of reports about the relevancy of Beta-arrestine1 and 2 in course of therapeutic treatment of HF in human necessitates to be determined. Recent reviewed studies about beta-arrestine1 and 2 and variant role as therapeutic implications [40].

### 1.4. Biased Agonism: At1r Receptors and Signaling

Self-regulating of cellular signal transduction across the membrane aptitude of the beta-arrestine has given rise to the phenomena biased agonism, which explains the subsequent activation of a single GPCR via more than one ligand which is distinctive subclasses downstream signaling actions. In accordance with that, ligand is categorizing as full agonists, inverse agonists, and neutral agonists as shown Figure-3 below [41, 42]. Biased ligands can selectively cause the activation of beta-arrestine regulatory pathway signaling devoid of activating G-protein signal transduction across membrane or block. Hence these ligands are named as biased agonist. Biased agonism and allosteric modulator has provided critical insight in considering pharmacology of GPCR and has providing better understanding to develop targeted and more effective treatment for GPCRs discerning signaling by ligand sketches, Over the time more biased agonist has been recognized for GPCRs which has distinctive well-adjusted agonist and have physiological effects, Beta1 adrenergic and beta2 adrenergic like among other subtypes of GPCRs are present across all mammalian heart including that of humans where it can influence cardiovascular system function In absence of any mechanical stress beta1 adrenergic is more scarce than that of beta2 adrenergic making up 80% and 20% (80:20) respectively of total beta adrenergic [42-44]. Moreover, in condition like heart failure this ratio becomes 60:20 as the specific repression of beta1 adrenergic by ligands. Beta endoergic are amongst receptors which plays an important role in regulation and influence myocardium is target of standard care therapy in daily practice [45]. Endogenously norepinephrine (neurotransmitter) and epinephrine (hormonal) are responsible for the activation of beta-adrenergic receptors. Hence a vital role in cardiovascular system regulation, such as increased myocardium contractility, cell survival signaling, increased in blood pressure due to aggravated Ang-II, myocardial hypertrophy and enhanced myocardium function all are effects of AT1R, TRV120023, and TRV 120027 when stimulated thru beta-arrestine biased ligand [46-49]. AT1R got attention for its role in advances and development of myocardium dysfunction caused by HF and G-alpha-q causes vasoconstriction when stimulated by signaling from G-protein [50, 51].and Hypertension while hypertrophy in cardiac myocytes [52, 53]. In some therapeutic context, use of AT1R and angiotensin enzymes inhibitors blocks

both the discorded signaling of G protein and beta-arrestine signaling of myocardium protective effects as well [54, 55]. Therefore, biased agonists are of great interest for studies in activation of beta-arrestine signaling by AT1R devoid of stimulating G protein which has then negative effect. Figure-3-4. New ligand of AT1R has been discovered in recent times that can mediate signaling of beta-arrestine. Work for development of AT1R mediated agonist ligands which act as beta-arrestine biases was some ten years ago started to create artificial analogous of angiotensin II as well as for sar-1, Ile-8-ang-II (SII) that target AT1R [56-58]. Moreover due to SII high specificity and poor affection, studies cannot concluded its biased mediation of signaling AT1R in myocardial cells, on the other hand specific interaction of beta-arrestine with AT1R have exhibited results in in vitro and erstwhile vivo studies, which then can cause activation of protein kinase pathways mediated by mitogen in G protein resulting enhances myocardial contractility, It has also enhance autonomous fashion Ca2+, it could be of potentially beneficent in myocardium [59, 60]. Another study conducted by Trevena Inc. in Chester brook Pennsylvania involved TRV023, TRV027, TRV067 and SII as central compound which mimic as biased ligand beta-arrestine including its effectiveness and specificity for AT1R and it the same time act as an antagonist for G protein signaling [61, 62]. Left ventricular pressure was elevated by AT1R signaling reliant on Beta-arrestine2 activation in mechanically induced diastolic expansion without the presence of Gq protein Langendorff perfused mice model. Moreover, there was marked elevation in level if ERK1/2 and phosphorylated Akt which inhibit the EGFR (epidermal growth factor receptors) [63]. In compliance of the verdicts, both beta-arrestine 1 and 2 mediated AT1R in vivo were responsible for the increase in contractility of left ventricle concomitant increase in volume. By this proportionate relation it designates that Frank Sterling mechanism in myocardium is sensitive to signaling stimulated by beta-arrestine [64]. In Addition to that in vitro model allosteric amplification were noted in affection and effectiveness of biased beta-arrestine orthosteric ligand of AT1R in osmotic expansion which recommends in mechanical stresses such as chronic Heart failure, force of contraction in left ventricle be able to enhanced AT1R agonist by biased beta-arrestine in vivo models of mice [65-68]. By combining all these outcomes Falker GM et al (Angiotensin-2 type1 receptors mediated by biased ligand in HF) conducted randomized double-blind placebo-controlled phase 2b (BLSDT-AHF) to find out the potentiality of biased ligands Beta-arrestine signaling at AT1R in deteriorating etiological heart failure. To evaluate TRV027 therapeutic effects in acute heart failure treatment. Body endured TRV027 well use of biased ligands in acute condition from 2 to 4 days intravenously infused has not favored desired results in controlled group compared to placebo over 30 days follow up clinical status remain the same [69, 70]. though it is still subject of importance in scientific community whether biased ligands at AT1R mediated by beta-arrestine was of benefits in chronic heart failure [71].

### 1.5. Biased Agonism: Bar Receptor and Signaling

Beta-adrenergic receptors are also of great importance while bearing in mind cardiovascular system. Beta1-adrengeric receptors enhanced the cardiac out by increasing heart rate, conduction velocity and stroke volume primarily accredited to signaling by G protein, while Beta2-adrenegic receptors influence the force of contraction (inotropic) of cardiac muscles and altered the tone of blood vessels. Beta1 and 2 adrenergic both are implied clinically in various condition relating to cardiovascular system [72]. In similar mechanism like biased signaling by biased beta arrestine at AT1R, Primarily Beta-adrenergic receptors result in activation of ERK ½ and epidermal growth factor receptors, and expounded for the advances of signaling transduction pathway survival pathways. Following studies have demonstrated that unmodulated beta adrenergic (orthosteric) ligand and beta blocker in combinations with carvedilol (used in clinical practices) activation of ERK ½ and epidermal growth factor receptors (EGFR) mediated by biased beta-arrestine without enhancing beta blocker prime function of action on G alpha-q protein [73, 74]. In retort carvedilol causes cardiac myocytes beta arrestine 2 tropisms granted by beta1 adrenergic via polymorphism phenomena in Arg-389-Gly revealed by latest studies. It states that natural phenomenon [75, 76]. Which emphasized on gene mutation in GPCRs may enhances mechanism of signaling in biased agonist [77]. In presences of carvedilol there has been amplification in miRNA (miR 214 and miR 199a 3p) in cardiac myocytes and subsequent cell survival signal modulation upon activation of protein kinase (Akt) mediated by micro-RNA at the same time suppress the genes responsible for apoptosis in myocardium, and this whole process is triggered when there is Beta1 adrenergic/beta arrestine1 biasedly stimulated by carvedilol in model of I/R. In same manner as biased agonism stated earlier, carvedilol enhanced significantly the formation of miRNA (miR-125b-5p) in mice myocardium leads to, rises protein kinase level again, repression of other type of genes amenable for apoptotic activity leading to enhance survival signal transduction in acute myocardial infarction [78]. In addition to that it was found in study micro RNA532 (miR532) of beta2 adrenergic and beta arrestine mainly responsible for suppression of enzyme serine protease 23 in endothelial cells of heart, reduced the conversion of EndMT (endothelial into mesenchymal) in model of myocardial infarction induces myocardium preservation [79]. conversely there was no clinical dissimilarly in treatment of heart failure amongst unbiased beta blocker (metoprolol) and biased ligand carvedilol published in meta-analysis [80]. it was indicated in study that in medicinal range carvedilol may not involve affectionately, and thus have no any well favors the patient, signaling interaction with beta arrestine [81]. To conclude the findings, whether or not unmodulated biased beta arrestine beta adrenergic ligands involves reportedly in regulations of myocardium contractility in similar mechanism, there is not enough data available about AT1R ligands because there is no other such combination of therapeutic efficacy beside carvedilol. As stated in early study by Kim IM et al, carvedilol induces micro RNA process in his action at beta adrenergic leading to stimulated activation of diverse signaling including that of across the membrane activation of epidermal growth factor receptors and stimulation of ERK mediated by beta arrestine These stimulated EGFRs thus have preserve myocardial tissues , In Lab mice, study in which gene responsible for the expression of beta1 adrenergic was

repressed, in absence of beta1 adrenergic, phosphorylation of GRK cannot be processed hence the interaction of Beta arrestine with EGFRs [82-84]. therefore, beta arrestine and signaling of beta adrenergic seems important in cardiac performance [85].

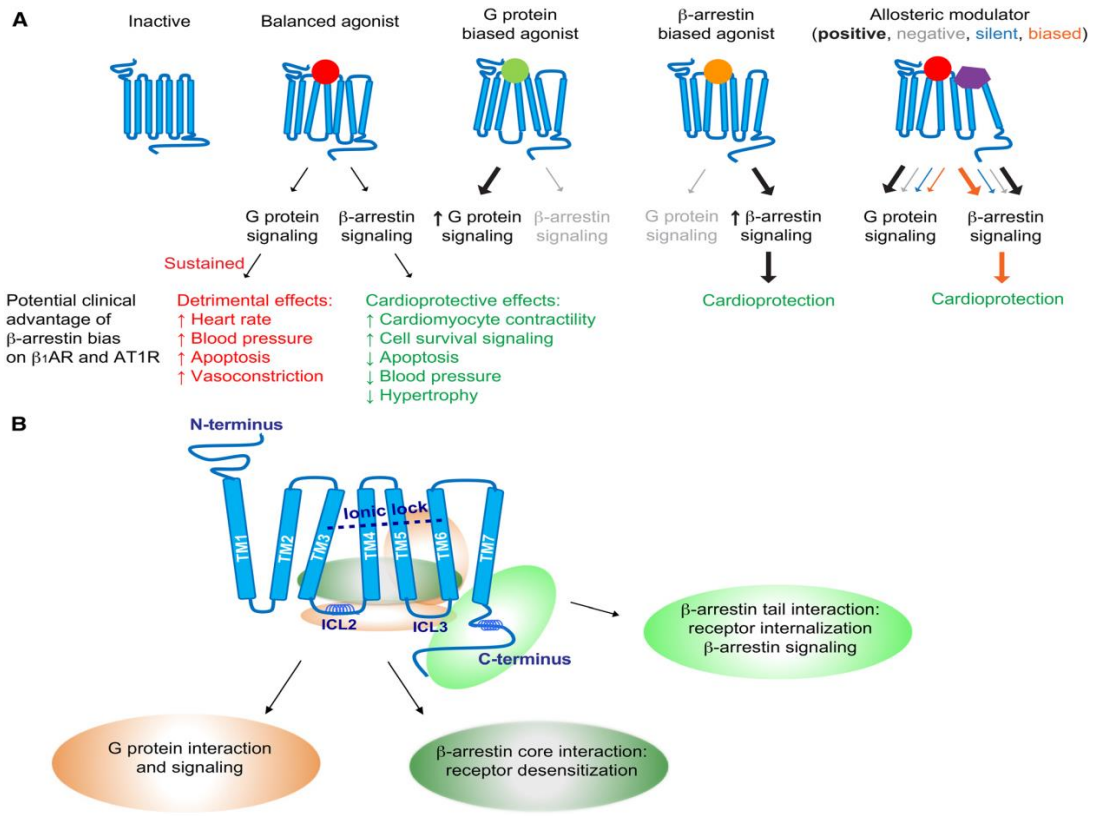


**Figure-3:** G-protein coupled receptor signaling

(A) Biased agonism by GPCRs potential clinical implication. Biased agonists specificity for G-protein or Beta-arrestine stimulated signaling pathway. Allosteric modulators bounded/ unbounded to its respective receptors and regulation of primary ligands. Studies in past suggest that beta1-adrenergic receptors activation of G-protein signaling has negative effects on cardiac myocytes, and beneficial effect of beta-arrestine on myocardium performance. Hence, blocking the activation of no G-protein effects by the action of beta1 adrenergic receptors, AT1R beta-arrestine agonist and allosteric stimulators results in boosting myocardium protective properties. (B); Essential aspects of GPCR structure are shown here. Biophysical studies have shown that how certain effectors stimulate GPCR structure in order to enhanced downstream signaling. In particulate transmembrane domain (TM3) and TM6 is particularly important for receptor activation upon release of iconic lock; Intracellular loop-2 (ICL-2), ICL-3, TM5 and TM6 give rise to the G-protein signaling; Beta-arrestine signaling has two distinct ways positioning (1); Receptor internalization by collaborating with receptor tail; (2); G-protein desensitization by collaborating with transmembrane core receptor.

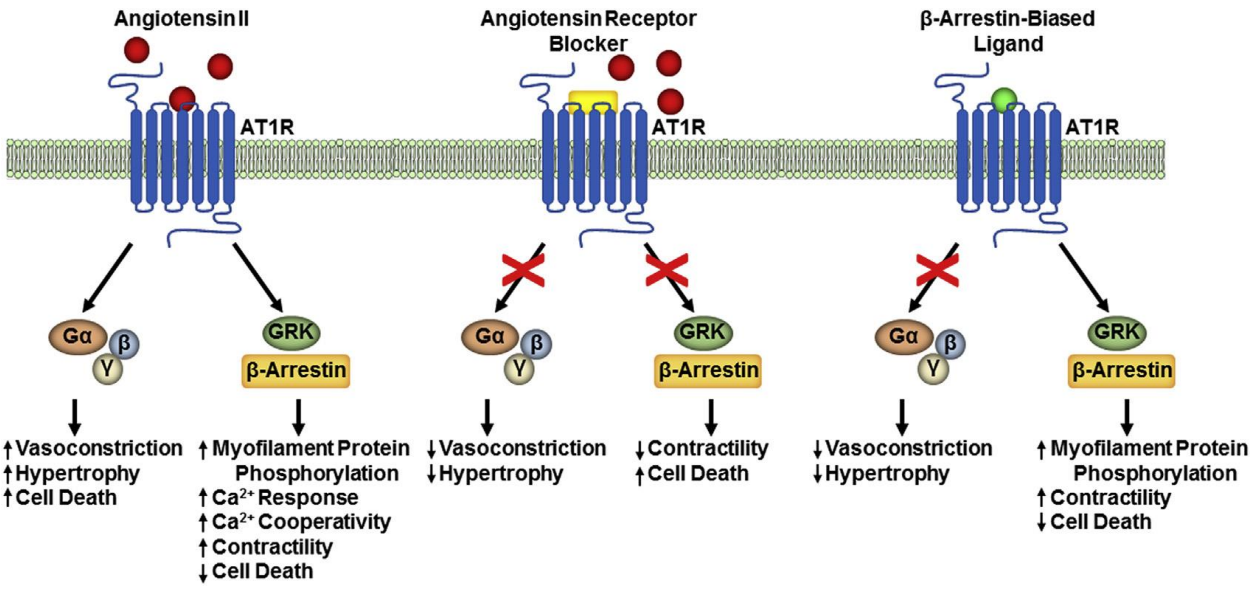


**Figure 4:** Physiological actions of agonism, Antagonism, and Biased agonism of AT1R of Cardiovascular system.

Above cartoon diagram shows the action of direct agonist versus antagonist; Biased agonism targeted by activity of beta-arrestine potentiality in comparison to Direct agonism and antagonism.

### 1.6. Alpha α-Adrenergic Receptors and Signaling

Alpha adrenergic receptors resembling beta adrenergic receptors, they are endogenously stimulated by catecholamine. Alpha adrenergic are family of Alpha1- α1A, α1B, α1D and Alpha2 contain α2A, α2B, α3B.Alpha1 receptors interacts initially with subunit alpha-q G protein activating phospholipase C, which causes the enhances rise in level of Ca2+ intracellulary by 2nd messenger formation inositol triphosphate 1, 4, 5 and diglyceride (DAG) stimulated by phospholipase-C. All the three α subtypes are mutually stimulates and regulates cardiac cells i-e alpha-1-A, alpha-1-B, in all of the subtype's alpha-1-B are widely distributed [147a] Alpha-1D receptors are widely distributed in smooth muscles of coronary artery as chief alpha-adrenergic subtype [86]. during unfavorable condition or under mechanical stress stimulus such as in hypertrophy/ protracted stimulation cause rise in expression of alpha-1 adrenergic in cardio myocytes, while alpha-1B and alpha-1D reduced in number, however total alpha adrenergic remain same or greater than before [87]. Alpha-1 adrenergic receptors are of great importance in myocardium preservation, physiological hypertrophy, enhances force of contraction, and concomitant reduction in apoptosis signal not similar to other alpha-q receptors G protein which have detrimental effects on cardiac myocytes in prolong activation and up regulation [88]. In study, repression of dual gene responsible for the alpha-1 and alpha-1B adrenergic receptors in transgenic mouse leads to the deteriorated dilated cardiomyopathy, rise in apoptotic activity, and decreased in survivance [89]. In clinical trials revels that before advising alpha-1 adrenergic agonist medication in hypertension and prostate abnormalities cautionary measures should be taken [90]. Alpa-1 adrenergic receptor agonist medications such as Prazosin and doxazosin hypertension lowering drugs but can leads to increase chances of Heart failure subsequent rise in mortality. Unlike cardio myocytes, Cardiac fibroblast lack alpha-1 adrenergic receptors [91, 92]. Alpha-1B might meditate new vessel formation (angiogenesis) and vasodilatation as they are distributed in endothelial cell of coronary artery [93, 94].

Alpha-2 adrenergic receptors reduced Ca2+ intracellulary by binding with Gαi, inhibit adenylyl cyclase subsequent decreases in cyclic adenosine monophosphate (cAMP), it can take place in both before synapses(presynaptic) and after synapses(postsynaptic). Before synapses (at presynaptic) alpha-2 adrenergic receptors mainly mediate the release of and sympathetic catecholamine at synapses. In absence of disease alpha-2 adrenergic activation mediated by norepinephrine has detrimental effect on release of norepinephrine [95]. in transgenic mouse models, study shown suppression of either genos responsible for alpha-2A and alpha-2C has leads to the increase of norepinephrine aggravate the heart failure [95]. Alpha-2B is responsible for the vasoconstriction as it is distributed in vascular smooth muscle cell [96, 97, 153].

### 1.7. Muscarinic Receptors and Signaling

Muscarinic receptors are widely distributed in human body and organs where they play an important role in pathophysiological processes such as stimulation of secretion from glands and contraction of smooth muscle cells. Aiming therapeutic medication at muscarinic receptors can of great purposes and has been vastly studied and explored, for the cardiovascular disease as well [98]. Muscarinic receptors comprised of five-5 subtypes namely M1, M2, M3, M4, and M5. Amongst all M1, M3, and M5 interact with Gq subunit and M2 and M2 bind to Gi. associated with diverse cardiac physiology. Among all M2 isoform is of importance in heart [99]. M2 receptor is responsible for inhibition of heart rate signal mediation of parasympathetic supply. moreover, acetylcholine activated M2 isoform interact with Gi protein decreases in cyclic adenosine monophosphate (cAMP) if current through hyperpolarized activated cyclic noontide gated ion channels [100]. reduction

in Ca2+ inside the cell [101, 102]. following detrimental inotropic chronotropic consequences [160]. At the same time G-beta and gamma subunits are responsible for further enhances detrimental chronotropic action at heterotetramer muscarinic gated potassium channels [103].

Muscarinic receptors were the first to recognized and studied in 90's to have biased activity in attempt of possible treatment for Alzheimer disease in which isoform M1 were stimulated by number of downstream signaling pathway. Latest studies have shown that non modulated, allosteric and other binding sites mutations in these open new ways to be targeted by therapeutic medication which is gaining interest in scientific community [104]. In addition to that pilocarpine medication used for the dry mouth and glaucoma is said to beta-arrestine biased ligand at M3 receptor [105, 106]. furthermore, diacylglycerol signal end and desensitization of M1 receptor by the action of beta arrestine and beta arrestine play a role molecular switch [107]. Thus, it looks very encouraging by pursuing to exploits the biased agonist at these receptors [108].

### 1.8. Endothelin Receptors and Signaling

here are total four-4 endothelin receptors ET1-4 out of these four Endothelin 1 is isoform chief situated in cardiovascular system. Prolong activation of Endothelin (ET) 1 can give rise to cardiac abnormities such as hypertrophy and hypertension [109, 110]. in transgenic models of heart failure there was mark elevation of endothelin (ET) 1 in plasma in both subjects. Endothelin (ET) can interact with one or the other G protein couple receptor Endothelin-A receptor (ETAR) or Endothelin-B receptor (ETBR) after couple with its receptors expressed itself [111, 112]. Though Endothelin-A receptor (ETAR) is said to be the key influencer and are responsible for the enhancement of inositol 1, 4, 5-trisphosphates (IP3) activity by interaction of Endothelin-A receptors (ETARs) with subunit Gq and activation of signal transduction in mitogen activated protein kinases (MAPK) in both atria and ventricle of heart. Endothelin-A receptors (ETARs) are seeming to be responsible for adenylyl cyclase inhibition probably by interacting with Gi [113]. moreover, in human blood vessels new biased ligands been identified could be related to hypertension. In experimentations in heart failure subject endothelin signal inhibition further life expectancy [114, 115]. but in human heart failure models' endothelin receptors inhibition is of no use in latest meta-analysis on clinical trials which examined four-endothelin receptors antagonist for the medicinal purposes [115-118]. Medication includes setaxentan, macitentan, bosentan and ambrisentan. Within each these medications have shown several critical adverse reactions. it is well known now that antagonist for endothelin receptor has preventive implication on cardiovascular system alongside it has shown some undesirable adverse reaction [119]. Development of certain medication to evade these unwanted results is of research interest. For this purpose, bosentan interaction with endothelin-B receptor crystal structure has been recently decrypted. in this investigation substantial linkage has been found amongst the two, presumably sustained as in closely affiliation with endothelin-A receptors (ETAR) [120]. The goal is for deeper knowledge of architecture correlation amongst receptor and its antagonist and determination for the development of potential therapeutic optimal drug delivery combination.

### 1.9. Adenosine Receptors and Signaling

A purine (Adenine base) adenosine has an important role in regulating physiological procedures, and to be found in cardiovascular system as well. G-protein coupled receptors known to mediate the function of adenosine over and done with receptors known as adenosine receptors (Adenosine A1 receptors). Presently it has four isoform adenosine1 receptor (A1R), adenosine2a receptor (A2aR), Adenosine2b Receptor (A2bR) and adenosine4 receptor (A3R). Adenosine interact with all of adenosine receptors (ARs) but the receptors are products are diverse in which sort of cell they are in what they mediation and they interaction with the effector. Adenosine-1 receptor and adenosine-3 receptor halts cyclic adenosine monophosphate by signal transduction through Gi while adenosine-2 receptors predominantly interact with Gs. AR stimulus and let go of G protein subunits Gβγ play substantial part in cell modification and growth.it is of no revelation because GPCRs have been mediated cause the release of Gβγ. [228a] adenosine-1 receptors known to have cause Ca2+ discharge, induce inositol trisphophate (IP3) and K+ and Ca2+ channel regulates in indirect manner. Like other biased GPCRs adenosine receptor have shown biased signal transduction such as novel ligand VCP746 decreases hypertrophy transgenic mice but show no results in human heart [121, 122]. Another partial agonist capadenoson which mediates adenosine1 receptors been able to modify heart failure in lab animal with heart failure in nonhuman species, while in fibroblasts and cardio myocytes adenosine-2b receptors mediates biased signaling [123]. [186a] Another example is of protraction of adenosine modulation by inosine which entertain adenosine-2 receptor in biased agonism. Adenosine-2 receptor mediates adenosine stimulation in vessels [124]. while adenosine-1 receptors stimulation by adenosine is responsible for cardio protection against reperfusion injuries, discourage detrimental numerous routes which leads to heart failure such as fibrosis, apoptosis, hypertrophy, ventricle dysfunction and arrythmogenesis induced by HF and enhances constructive effects against heart failure [125]. Pharmacological objective aims at adenosine-1 receptors, there are numerous agonist and antagonist are considered in heart failure [126, 127]. for this purposes rolofylline (KW 3902) an experimental antagonist of adenosine-1 receptor [128]. Use of this medication restricted it use due to stroke occurrence in subjects in spite of relieving of symptoms in renal impairment [129, 130]. contradictory to that, agonist for adenosine-1 efficaciously stabilizes heart rate in arrhythmias [131]. in chronic heart failure shows no adverse reaction [131]. Currently use of partial agonist is of great interest [132]. At present aim of using partial agonist for the activation of receptors without provoking diverse action and ascertaining of the biased ligand [133]. Nevertheless, aiming at adenosine-1 receptors which is situated in heart and adenosine-2 receptors are in vessels. And both have potential to be used therapeutically but bear in mind the partial agonist specificity of biased ligands and for its subtype as well.

## 1.10. Apelin/Apj Receptor System and Signaling

Apelin/APJ system is novel G protein couple receptor APJ are widely distributed in heart, central nervous system and periphery tissues and was discovered in 1998 formerly known as APJ orphan receptor is now attention for target therapeutic therapy in various tissue including heart. An analogous to angiotensin1 receptors, and has similar distribution. Apelin formed as pre-pro apelin and split into numerous small segments by the action of ACE (angiotensin converting enzyme) [134, 135]. These small fragments are diverse activity and can stimulate, endocytosis, and reuse of ligands. APJ interact with Gi subunit of G protein GPCR and have capability to bind with Gq Apelin have a wide range of role in regulating across both cardiovascular system and periphery tissues, including stimulates constriction of vessels, formation of new blood vessel and alters muscular contraction force (inotropic agent) [134, 136-138]. In vascular system Apelin counteract angiotensin 1 receptors activity by interacting with Gi which causes nitric acid to release. Apelin is effectively amends cardiac contraction (inotropic agent), and stimulate PKC or PLC, sarcolemmal NHE (Na+-H+) exchange, pathways Na+-Ca2+ by Gq activation though they are abstemiously distributed in Heart [139-142]. APJ mediators either endogenous mediators, or small apelin segment act as biased ligand Though receptor internalization carried out by mediation of beta arrestine [143-146]. Which can give rise to hypertrophy if APJ activation occurs by distention [146]. In cardiac dysfunction patients increased in Apelin/APJ plasma level were observed initially and in later stages declined [145]. In lab, induced ischemic heart failure (IHF) in murine animal models there was sudden overexpression of Apelin/APJ subsequently by ischemic injury. The aforesaid changes remain for long time [147]. Suppressions of gene responsible for Apelin/APJ in mouse results abnormalities in contraction I/R injury delayed recovery [148-152]. moreover, dosing Apelin or apelin analogues prevents I/R in induced ICH (ischemic heart diseases) rodent lab animal models [153]. Encouraging its possible therapeutic use in heart failure specifically aiming at Apelin/AJP. [150,160d] Nevertheless biased ligand for apelin/APJ receptor system yet to be resolute.

## 1.11. Other Gpcrs

There are more than two hundred G-protein couple receptors expressed in human heart Apart from the aforementioned receptors, there are numerous other prominent receptors which influences progression or management of cardiovascular diseases, such as 5-hydroxytryptmine receptor 2b (Serotonin 5-HT2b) stimulates heart muscles growth and function, while enhances fibrosis and hypertrophy in heart upon activation [154]. In chronic heart failure histamine type 2 receptors (H2R) antagonist ameliorate heart function [155, 156]. Relaxin (the peptide hormone) and its receptors actions enhances the anti-fibrosis and cardio protecting activity. Recombinant human Relaxin 2 hormone (serelaxin) is still under investigation intended for treatment of critical heart failure [157]. in induced heart failure for investigation purpose, inhibition of arginine vasopressin receptor 2 (AVPR2) minimizes renal impairment and cardiac dysfunction [158]. Cardiac lysosphingolipids (Sphingosine 1 phosphate) receptors stimulation known to influences cardio protection [159]. Figure-5 shows the GPCRs and its effects on cardiovascular system [160].

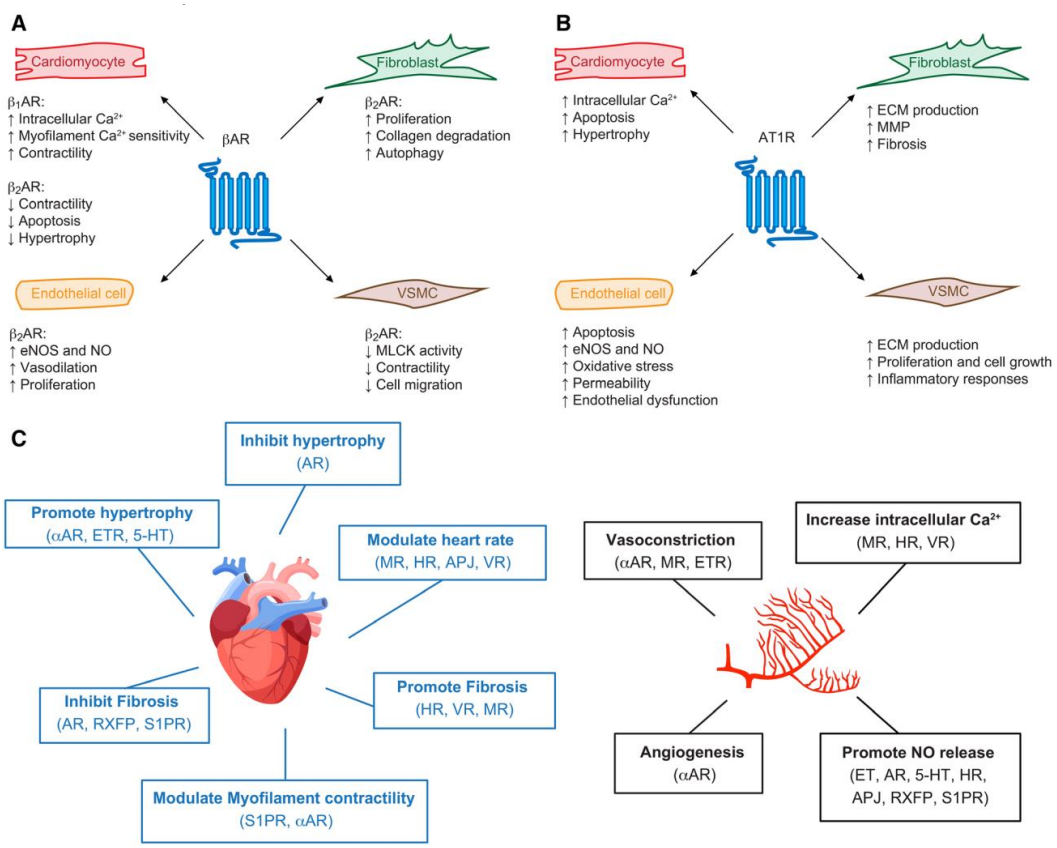


**Figure 5:** G protein couple receptors in cardiovascular system and its function

## 2. Conclusion

cardiovascular diseases (CVD) take estimated 17.9 million life's annually and leading cause of death worldwide. Comprehension the structure and function of G protein couple receptors and influence over the physiological pathophysiological is subject of great interest for therapeutic targeted therapy against the said receptor and improve specificity of biased ligand at their respective receptors in cardiovascular diseases especially in heart failure. Moreover, unlike in traditional pharmacology in which diverse approach (agonists and Antagonist) towards receptor, is now being substituting by more targeted approach, henceforth enhances the signaling focused at ligand. For case in point in-silico molecular docking bio active (peptides/ chemical drug) delivery and binding specificity (structural based drugs) with the receptors, it is achieved through investigational studies of GPCR structure in Biophysics. Lack of information about the structure of GPCR as well as GPCRs understanding, fragility, and short duration of the receptor-activator was main hurdles in past. At present major advances in technology such as transmission electron cryomicroscopy (CryoEM), has led to the better understanding of anti-body based therapeutic targeting of GPCR, to engage specific receptor and to have desired effects for example single-domain antibody (Nano body) and antigen binding fragments (Fab). Biased agonism is receiving interest for therapeutic purposes, accomplish at minimal unwanted effects is fetching reality in sub atomic and molecular level to modulate downstream signaling pathways. As more and more progress in technological and methodological would provide with better diverse structural /function of GPCR and can lead to innovation of therapeutic drugs that are more specific or biased in their function by enhances/inhibiting receptors in cardiovascular disease thus minimizing adverse effects. As of now there are numerous orphan receptors yet to be characterized in cardiovascular system. Novel ligand and mechanism of action for GPCRs has been established and need vigorous experiments which may one day lead to development of innovative therapeutic stratagems.

## References


1. Benjamin, E. J., Virani, S. S., Callaway, C. W., Chamberlain, A. M., Chang, A. R., et al. (2018). Heart disease and stroke statistics—2018 update: a report from the American Heart Association. Circulation, 137(12), e67-e492.
2. Tanai, E., & Frantz, S. (2011). Pathophysiology of heart failure. Comprehensive physiology, 6(1), 187-214.
3. Yancy, C. W., Jessup, M., Bozkurt, B., Butler, J., Casey Jr, D. E., et al. 20İ3 ACCF/AHA guideline for the management of heart failure: Executive summary: A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation, 128, İ8İ0-İ852.
4. Venkatakrishnan, A. J., Deupi, X., Lebon, G., Tate, C. G., Schertler, G. F., et al. (2013). Molecular signatures of G-protein-coupled receptors. Nature, 494(7436), 185-194.
5. Congreve, M., de Graaf, C., Swain, N. A., & Tate, C. G. (2020). Impact of GPCR structures on drug discovery. Cell, 181(1), 81-91.
6. Zhu, W., Woo, A. Y. H., Zhang, Y., Cao, C. M., & Xiao, R. P. (2011). β-adrenergic receptor subtype signaling in the heart: from bench to the bedside. Current topics in membranes, 67, 191-204.
7. Arang, N., & Gutkind, J. S. (2020). G Protein-Coupled receptors and heterotrimeric G proteins as cancer drivers. FEBS letters, 594(24), 4201-4232.
8. Hillenbrand, M., Schori, C., Schöppe, J., & Plückthun, A. (2015). Comprehensive analysis of heterotrimeric G-protein complex diversity and their interactions with GPCRs in solution. Proceedings of the National Academy of Sciences, 112(11), E1181-E1190.
9. Pleli, T., Mondorf, A., Ferreiros, N., Thomas, D., Dvorak, K., et al. (2018). Activation of adenylyl cyclase causes stimulation of adenosine receptors. Cellular Physiology and Biochemistry, 45(6), 2516-2528.
10. Pierce, K. L., Premont, R. T., & Lefkowitz, R. J. (2002). Seven-transmembrane receptors. Nature reviews Molecular cell biology, 3(9), 639-650.
11. Newton, A. C. (1997). Regulation of protein kinase C. Curr Opin Cell Biol.
12. Kozasa, T., Jiang, X., Hart, M. J., Sternweis, P. M., Singer, W. D., Gilman, A. G., et al. (1998). p115 RhoGEF, a GTPase activating protein for Gα12 and Gα13. Science, 280(5372), 2109-2111.
13. Irannejad, R., Tomshine, J. C., Tomshine, J. R., Chevalier, M., Mahoney, J. P., et al. (2013). Conformational biosensors reveal GPCR signalling from endosomes. Nature, 495(7442), 534-538.
14. Boivin, B., Lavoie, C., Vaniotis, G., Baragli, A., Villeneuve, L. R., et al. (2006). Functional β-adrenergic receptor signalling on nuclear membranes in adult rat and mouse ventricular cardiomyocytes. Cardiovascular research, 71(1), 69-78.
15. Pessentheiner, A. R., Pelzmann, H. J., Walenta, E., Schweiger, M., Groschner, L. N., et al. (2013). NAT8L (N-acetyltransferase 8-like) accelerates lipid turnover and increases energy expenditure in brown adipocytes. Journal of Biological Chemistry, 288(50), 36040-36051.
16. Wright, C. D., Chen, Q., Baye, N. L., Huang, Y., Healy, C. L., et al. (2008). Nuclear α1-adrenergic receptors signal activated ERK localization to caveolae in adult cardiac myocytes. Circulation research, 103(9), 992-1000.
17. Rockman, H. A., Koch, W. J., & Lefkowitz, R. J. (2002). Seven-transmembrane-spanning receptors and heart function. Nature, 415(6868), 206-212.
18. Marinissen, M. J., & Gutkind, J. S. (2001). G-protein-coupled receptors and signaling networks: emerging paradigms. Trends in pharmacological sciences, 22(7), 368-376.
19. Kelly, E., Bailey, C. P., & Henderson, G. (2008). Agonist-selective mechanisms of GPCR desensitization. British journal of pharmacology, 153(S1), S379-S388.
20. Shi, Q., Li, M., Mika, D., Fu, Q., Kim, S., et al. (2017). Heterologous desensitization of cardiac β-adrenergic signal via hormone-induced βAR/arrestin/PDE4 complexes. Cardiovascular research, 113(6), 656-670.
21. Perry, S. J., Baillie, G. S., Kohout, T. A., McPhee, I., Magiera, M. M., et al. (2002). Targeting of cyclic AMP degradation to

β2-adrenergic receptors by β-arrestins. Science, 298(5594), 834-836.
22. Baillie, G. S., Sood, A., McPhee, I., Gall, I., Perry, S. J., et al. (2003). β-Arrestin-mediated PDE4 cAMP phosphodiesterase recruitment regulates β-adrenoceptor switching from Gs to Gi. Proceedings of the National Academy of Sciences, 100(3), 940-945.
23. Rajagopal, S., & Shenoy, S. K. (2018). GPCR desensitization: Acute and prolonged phases. Cellular signalling, 41, 9-16.
24. Eichel, K., Jullié, D., Barsi-Rhyne, B., Latorraca, N. R., Masureel, M., et al. (2018). Catalytic activation of β-arrestin by GPCRs. Nature, 557(7705), 381-386.
25. Shukla, A. K., Westfield, G. H., Xiao, K., Reis, R. I., Huang, L. Y., et al. (2014). Visualization of arrestin recruitment by a G-protein-coupled receptor. Nature, 512(7513), 218-222.
26. Oakley, R. H., Laporte, S. A., Holt, J. A., Barak, L. S., & Caron, M. G. (1999). Association of β-arrestin with G protein-coupled receptors during clathrin-mediated endocytosis dictates the profile of receptor resensitization. Journal of Biological Chemistry, 274(45), 32248-32257.
27. Thomsen, A. R., Plouffe, B., Cahill, T. J., Shukla, A. K., Tarrasch, J. T., et al. (2016). GPCR-G protein-β-arrestin super-complex mediates sustained G protein signaling. Cell, 166(4), 907-919.
28. Shenoy, S. K., & Lefkowitz, R. J. (2011). β-Arrestin-mediated receptor trafficking and signal transduction. Trends in pharmacological sciences, 32(9), 521-533.
29. Shukla, A. K., Xiao, K., & Lefkowitz, R. J. (2011). Emerging paradigms of β-arrestin-dependent seven transmembrane receptor signaling. Trends in biochemical sciences, 36(9), 457-469.
30. Hirsch, J. A., Schubert, C., Gurevich, V. V., & Sigler, P. B. (1999). The 2.8 A crystal structure of visual arrestin: a model for arrestin's regulation. Cell, 97(2), 257-270.
31. Han, M., Gurevich, V. V., Vishnivetskiy, S. A., Sigler, P. B., & Schubert, C. (2001). Crystal structure of β-arrestin at 1.9 Å: possible mechanism of receptor binding and membrane translocation. Structure, 9(9), 869-880.
32. LM, L. (1999). Beta-arrestin-dependent formation of beta2 adrenergic receptor-Src protein kinase complexes. Science, 283, 655-661.
33. Noma, T., Lemaire, A., Prasad, S. V. N., Barki-Harrington, L., Tilley, D. G., et al. (2007). β-arrestin–mediated β 1-adrenergic receptor transactivation of the EGFR confers cardioprotection. The Journal of clinical investigation, 117(9), 2445-2458.
34. Kim, J., Ahn, S., Rajagopal, K., & Lefkowitz, R. J. (2009). Independent β-arrestin2 and Gq/protein kinase Cζ pathways for ERK stimulated by angiotensin type 1A receptors in vascular smooth muscle cells converge on transactivation of the epidermal growth factor receptor. Journal of Biological Chemistry, 284(18), 11953-11962.
35. DeWire, S. M., Kim, J., Whalen, E. J., Ahn, S., Chen, M., et al. (2008). β-Arrestin-mediated signaling regulates protein synthesis. Journal of Biological Chemistry, 283(16), 10611-10620.
36. Ahn, S., Kim, J., Hara, M. R., Ren, X. R., & Lefkowitz, R. J. (2009). β-Arrestin-2 mediates anti-apoptotic signaling through regulation of BAD phosphorylation. Journal of Biological Chemistry, 284(13), 8855-8865.
37. Ahn, S., Shenoy, S. K., Wei, H., & Lefkowitz, R. J. (2004). Differential kinetic and spatial patterns of β-arrestin and G protein-mediated ERK activation by the angiotensin II receptor. Journal of Biological Chemistry, 279(34), 35518-35525.
38. Tilley, D. G., Kim, I. M., Patel, P. A., Violin, J. D., & Rockman, H. A. (2009). β-Arrestin mediates β1-adrenergic receptor-epidermal growth factor receptor interaction and downstream signaling. Journal of Biological Chemistry, 284(30), 20375-20386.
39. Sterne-Marr, R., Dhami, G. K., Tesmer, J. J., & Ferguson, S. S. (2004). Characterization of GRK2 RH domain-dependent regulation of GPCR coupling to heterotrimeric G proteins. Methods in enzymology, 390, 310-336.
40. Wang, Y., Jin, L., Song, Y., Zhang, M., Shan, D., et al. (2017). β-arrestin 2 mediates cardiac ischemia-reperfusion injury via inhibiting GPCR-independent cell survival signalling. Cardiovascular research, 113(13), 1615-1626.
41. Zhabyeyev, P., Zhang, H., & Oudit, G. Y. (2017). Is β-arrestin 2 a magic bullet for heart failure treatment? Hypertension, 70(5), 887-889.
42. Rajagopal, S., Rajagopal, K., & Lefkowitz, R. J. (2010). Teaching old receptors new tricks: biasing seven-transmembrane receptors. Nature reviews Drug discovery, 9(5), 373-386.
43. Violin, J. D., & Lefkowitz, R. J. (2007). β-Arrestin-biased ligands at seven-transmembrane receptors. Trends in pharmacological sciences, 28(8), 416-422.
44. Violin, J. D., Soergel, D. G., Boerrigter, G., Burnett Jr, J. C., & Lark, M. W. (2013). GPCR biased ligands as novel heart failure therapeutics. Trends in cardiovascular medicine, 23(7), 242-249.
45. Woo, A. Y. H., & Xiao, R. P. (2012). β-Adrenergic receptor subtype signaling in heart: from bench to bedside. Acta Pharmacologica Sinica, 33(3), 335-341.
46. Salazar, N. C., Chen, J., & Rockman, H. A. (2007). Cardiac GPCRs: GPCR signaling in healthy and failing hearts. Biochimica et Biophysica Acta (BBA)-Biomembranes, 1768(4), 1006-1018.
47. Violin, J. D., DeWire, S. M., Yamashita, D., Rominger, D. H., Nguyen, et al. (2010). Selectively engaging β-arrestins at the angiotensin II type 1 receptor reduces blood pressure and increases cardiac performance. Journal of Pharmacology and Experimental Therapeutics, 335(3), 572-579.
48. Boerrigter, G., Lark, M. W., Whalen, E. J., Soergel, D. G., Violin, J. D., et al. (2011). Cardiorenal actions of TRV120027, a novel ß-arrestin–biased ligand at the angiotensin II type I receptor, in healthy and heart failure canines: a novel therapeutic strategy for acute heart failure. Circulation: Heart Failure, 4(6), 770-778.
49. Kim, K. S., Abraham, D., Williams, B., Violin, J. D., Mao, L., (2012). β-Arrestin-biased AT1R stimulation promotes cell survival during acute cardiac injury. American Journal of Physiology-Heart and Circulatory Physiology, 303(8), H1001-H1010.
50. Monasky, M. M., Taglieri, D. M., Henze, M., Warren,

C. M., Utter, M. S., et al. (2013). The β-arrestin-biased ligand TRV120023 inhibits angiotensin II-induced cardiac hypertrophy while preserving enhanced myofilament response to calcium. American Journal of Physiology-Heart and Circulatory Physiology, 305(6), H856-H866.
51. Kim, J., Eckhart, A. D., Eguchi, S., & Koch, W. J. (2002). β-adrenergic receptor-mediated DNA synthesis in cardiac fibroblasts is dependent on transactivation of the epidermal growth factor receptor and subsequent activation of extracellular signal-regulated kinases. Journal of Biological Chemistry, 277(35), 32116-32123.
52. Aránguiz-Urroz, P., Canales, J., Copaja, M., Troncoso, R., Vicencio, J. M., et al. (2011). Beta2-adrenergic receptor regulates cardiac fibroblast autophagy and collagen degradation. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 1812(1), 23-31.
53. Rajagopal, S., Rajagopal, K., & Lefkowitz, R. J. (2010). Teaching old receptors new tricks: biasing seven-transmembrane receptors. Nature reviews Drug discovery, 9(5), 373-386.
54. Violin, J. D., DeWire, S. M., Barnes, W. G., & Lefkowitz, R. J. (2006). G protein-coupled receptor kinase and β-arrestin-mediated desensitization of the angiotensin II type 1A receptor elucidated by diacylglycerol dynamics. Journal of Biological Chemistry, 281(47), 36411-36419.
55. Hoogwerf, B. J. (2010). Renin–angiotensin system blockade and cardiovascular and renal protection. The American journal of cardiology, 105(1), 30A-35A.
56. Mercier, K., Smith, H., & Biederman, J. (2014). Renin-angiotensin-aldosterone system inhibition: overview of the therapeutic use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, and direct renin inhibitors. Primary Care: Clinics in Office Practice, 41(4), 765-778.
57. Wei, H., Ahn, S., Shenoy, S. K., Karnik, S. S., Hunyady, L., et al. (2003). Independent β-arrestin 2 and G protein-mediated pathways for angiotensin II activation of extracellular signal-regulated kinases 1 and 2. Proceedings of the National Academy of Sciences, 100(19), 10782-10787.
58. Ahn, S., Shenoy, S. K., Wei, H., & Lefkowitz, R. J. (2004). Differential kinetic and spatial patterns of β-arrestin and G protein-mediated ERK activation by the angiotensin II receptor. Journal of Biological Chemistry, 279(34), 35518-35525.
59. Kim, J., Ahn, S., Rajagopal, K., & Lefkowitz, R. J. (2009). Independent beta-arrestin2 and 609 Gq/protein kinase Czeta pathways for ERK stimulated by angiotensin type 1A receptors in 610 vascular smooth muscle cells converge on transactivation of the epidermal growth factor 611 receptor. J Biol Chem, 284(11953-11962), 612.
60. Rajagopal, K., Whalen, E. J., Violin, J. D., Stiber, J. A., Rosenberg, P. B., et al. (2006). β-Arrestin2-mediated inotropic effects of the angiotensin II type 1A receptor in isolated cardiac myocytes. Proceedings of the National Academy of Sciences, 103(44), 16284-16289.
61. Aplin, M., Christensen, G. L., Schneider, M., Heydorn, A., Gammeltoft, S., et al. (2007). The angiotensin type 1 receptor activates extracellular signal-regulated kinases 1 and 2 by G protein-dependent and-independent pathways in cardiac myocytes and langendorff-perfused hearts. Basic & clinical pharmacology & toxicology, 100(5), 289-295.
62. Violin, J. D., DeWire, S. M., Yamashita, D., Rominger, D. H., Nguyen, L., et al. (2010). Selectively engaging β-arrestins at the angiotensin II type 1 receptor reduces blood pressure and increases cardiac performance. Journal of Pharmacology and Experimental Therapeutics, 335(3), 572-579.
63. Kim, K. S., Abraham, D., Williams, B., Violin, J. D., Mao, L., et al. (2012). β-Arrestin-biased AT1R stimulation promotes cell survival during acute cardiac injury. American Journal of Physiology-Heart and Circulatory Physiology, 303(8), H1001-H1010.
64. Rakesh, K., Yoo, B., Kim, I. M., Salazar, N., Kim, K. S., et al. (2010). β-arrestin–biased agonism of the angiotensin receptor induced by mechanical stress. Science signaling, 3(125), ra46-ra46.
65. Abraham, D. M., Davis III, R. T., Warren, C. M., Mao, L., Wolska, B. M., et al. (2016). β-Arrestin mediates the Frank–Starling mechanism of cardiac contractility. Proceedings of the National Academy of Sciences, 113(50), 14426-14431.
66. Tang, W., Strachan, R. T., Lefkowitz, R. J., & Rockman, H. A. (2014). Allosteric modulation of β-arrestin-biased angiotensin II type 1 receptor signaling by membrane stretch. Journal of Biological Chemistry, 289(41), 28271-28283.
67. Ryba, D. M., Li, J., Cowan, C. L., Russell, B., Wolska, B. M., et al. (2017). Long-term biased β-arrestin signaling improves cardiac structure and function in dilated cardiomyopathy. Circulation, 135(11), 1056-1070.
68. Monasky, M. M., Taglieri, D. M., Henze, M., Warren, C. M., Utter, M. S., et al. (2013). The β-arrestin-biased ligand TRV120023 inhibits angiotensin II-induced cardiac hypertrophy while preserving enhanced myofilament response to calcium. American Journal of Physiology-Heart and Circulatory Physiology, 305(6), H856-H866.
69. Tarigopula, M., Davis 3rd, R. T., Mungai, P. T., Ryba, D. M., Wieczorek, D. F., et al. (2015). Cardiac myosin light chain phosphorylation and inotropic effects of a biased ligand, TRV120023, in a dilated cardiomyopathy model. Cardiovascular Research, 107(2), 226-234.
70. Felker, G. M., Butler, J., Collins, S. P., Cotter, G., Davison, B. A., et al. (2015). Heart failure therapeutics on the basis of a biased ligand of the angiotensin-2 type 1 receptor: rationale and design of the BLAST-AHF study (Biased Ligand of the Angiotensin Receptor Study in Acute Heart Failure). JACC: Heart Failure, 3(3), 193-201.
71. Soergel, D. G., Subach, R. A., Cowan, C. L., Violin, J. D., & Lark, M. W. (2013). First clinical experience with TRV027: pharmacokinetics and pharmacodynamics in healthy volunteers. The Journal of Clinical Pharmacology, 53(9), 892-899.
72. Pang, P. S., Butler, J., Collins, S. P., Cotter, G., Davison, B. A., Ezekowitz, J. A., et al. (2017). Biased ligand of the angiotensin II type 1 receptor in patients with acute heart failure: a randomized, double-blind, placebo-controlled,

phase IIB, dose ranging trial (BLAST-AHF). European heart journal, 38(30), 2364-2373.
73. Lohse, M. J., Engelhardt, S., & Eschenhagen, T. (2003). What is the role of β-adrenergic signaling in heart failure? Circulation research, 93(10), 896-906.
74. Noma, T., Lemaire, A., Prasad, S. V. N., Barki-Harrington, L., Tilley, D. G., et al. (2007). β-arrestin–mediated β 1-adrenergic receptor transactivation of the EGFR confers cardioprotection. The Journal of clinical investigation, 117(9), 2445-2458.
75. Maudsley, S., Pierce, K. L., Zamah, A. M., Miller, W. E., Ahn, S., et al. (2000). The β2-adrenergic receptor mediates extracellular signal-regulated kinase activation via assembly of a multi-receptor complex with the epidermal growth factor receptor. Journal of Biological Chemistry, 275(13), 9572-9580.
76. Kim, I. M., Tilley, D. G., Chen, J., Salazar, N. C., Whalen, E. J., et al. (2008). β-Blockers alprenolol and carvedilol stimulate β-arrestin-mediated EGFR transactivation. Proceedings of the National Academy of Sciences, 105(38), 14555-14560.
77. Wisler, J. W., DeWire, S. M., Whalen, E. J., Violin, J. D., Drake, M. T., et al. (2007). A unique mechanism of β-blocker action: carvedilol stimulates β-arrestin signaling. Proceedings of the National Academy of Sciences, 104(42), 16657-16662.
78. McCrink, K. A., Brill, A., Jafferjee, M., Valero, T. R., Marrero, C., et al. (2016). β1-adrenoceptor Arg389Gly polymorphism confers differential β-arrestin-binding tropism in cardiac myocytes. Pharmacogenomics, 17(15), 1611-1620.
79. Park, K. M., Teoh, J. P., Wang, Y., Broskova, Z., Bayoumi, A. S., et al. (2016). Carvedilol-responsive microRNAs, miR-199a-3p and-214 protect cardiomyocytes from simulated ischemia-reperfusion injury. American Journal of Physiology-Heart and Circulatory Physiology, 311(2), H371-H383.
80. Bayoumi, A. S., Park, K. M., Wang, Y., Teoh, J. P., Aonuma, T., et al. (2018). A carvedilol-responsive microRNA, miR-125b-5p protects the heart from acute myocardial infarction by repressing pro-apoptotic bak1 and klf13 in cardiomyocytes. Journal of molecular and cellular cardiology, 114, 72-82.
81. Bayoumi, A. S., Teoh, J. P., Aonuma, T., Yuan, Z., Ruan, X., et al. (2017). MicroRNA-532 protects the heart in acute myocardial infarction, and represses prss23, a positive regulator of endothelial-to-mesenchymal transition. Cardiovascular research, 113(13), 1603-1614.
82. Briasoulis, A., Palla, M., & Afonso, L. (2015). Meta-analysis of the effects of carvedilol versus metoprolol on all-cause mortality and hospitalizations in patients with heart failure. The American journal of cardiology, 115(8), 1111-1115.
83. Tilley, D. G., Kim, I. M., Patel, P. A., Violin, J. D., & Rockman, H. A. (2009). β-Arrestin mediates β1-adrenergic receptor-epidermal growth factor receptor interaction and downstream signaling. Journal of Biological Chemistry, 284(30), 20375-20386.
84. Kim, I. M., Tilley, D. G., Chen, J., Salazar, N. C., Whalen, E. J., et al. (2008). β-Blockers alprenolol and carvedilol stimulate β-arrestin-mediated EGFR transactivation. Proceedings of the National Academy of Sciences, 105(38), 14555-14560.
85. Kim, I. M., Wang, Y., Park, K. M., Tang, Y., Teoh, J. P., et al. (2014). β-arrestin1–biased β1-adrenergic receptor signaling regulates microRNA processing. Circulation research, 114(5), 833-844.
86. Noma, T., Lemaire, A., Prasad, S. V. N., Barki-Harrington, L., Tilley, D. G., et al. (2007). β-arrestin–mediated β 1-adrenergic receptor transactivation of the EGFR confers cardioprotection. The Journal of clinical investigation, 117(9), 2445-2458.
87. O'Connell, T. D., Jensen, B. C., Baker, A. J., & Simpson, P. C. (2014). Cardiac alpha1-adrenergic receptors: novel aspects of expression, signaling mechanisms, physiologic function, and clinical importance. Pharmacological reviews, 66(1), 308-333.
88. Jensen, B. C., Swigart, P. M., Laden, M. E., DeMarco, T., Hoopes, C., et al. (2009). The alpha-1D Is the predominant alpha-1-adrenergic receptor subtype in human epicardial coronary arteries. Journal of the American College of Cardiology, 54(13), 1137-1145.
89. O'Connell, T. D., Ishizaka, S., Nakamura, A., Swigart, P. M., Rodrigo, M. C., et al. (2003). The α 1A/C-and α 1B-adrenergic receptors are required for physiological cardiac hypertrophy in the double-knockout mouse. The Journal of clinical investigation, 111(11), 1783-1791.
90. McCloskey, D. T., Turnbull, L., Swigart, P., O'Connell, T. D., Simpson, P. C., et al. (2003). Abnormal Myocardial Contraction in α1A–and α1B–adrenoceptor double-knockout mice. Journal of molecular and cellular cardiology, 35(10), 1207-1216.
91. O'Connell, T. D., Swigart, P. M., Rodrigo, M. C., Ishizaka, S., Joho, S., et al. (2006). α 1-Adrenergic receptors prevent a maladaptive cardiac response to pressure overload. The Journal of clinical investigation, 116(4), 1005-1015.
92. Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Collaborative Research Group. Diuretic versus alpha-blocker as first-step antihypertensive therapy: final results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Hypertension. 2003; 42:239–246. Doi: 10.1161/01.HYP. 0000086521.95630.5A
93. Cohn, J. N. (1993). The Vasodilator-Heart Failure Trials (V-HeFT). Mechanistic data from the VA Cooperative Studies. Introduction. Circulation, 87(6 Suppl), VI1-4.
94. Stewart, A. F., Rokosh, D. G., Bailey, B. A., Karns, L. R., Chang, K. C., et al. (1994). Cloning of the rat alpha 1C-adrenergic receptor from cardiac myocytes. alpha 1C, alpha 1B, and alpha 1D mRNAs are present in cardiac myocytes but not in cardiac fibroblasts. Circulation research, 75(4), 796-802.
95. Jensen, B. C., Swigart, P. M., Montgomery, M. D., & Simpson, P. C. (2010). Functional alpha-1B adrenergic receptors on human epicardial coronary artery endothelial cells. Naunyn-Schmiedeberg's archives of pharmacology, 382, 475-482.

96. Hein, L., Altman, J. D., & Kobilka, B. K. (1999). Two functionally distinct α2-adrenergic receptors regulate sympathetic neurotransmission. Nature, 402(6758), 181-184.
97. Brede, M., Wiesmann, F., Jahns, R., Hadamek, K., Arnolt, C., et al. (2002). Feedback inhibition of catecholamine release by two different α2-adrenoceptor subtypes prevents progression of heart failure. Circulation, 106(19), 2491-2496.
98. Brede, M., Nagy, G., Philipp, M., Sørensen, J. B., Lohse, M. J., et al. (2003). Differential control of adrenal and sympathetic catecholamine release by α2-adrenoceptor subtypes. Molecular endocrinology, 17(8), 1640-1646.
99. Matera, C., & M Tata, A. (2014). Pharmacological approaches to targeting muscarinic acetylcholine receptors. Recent Patents on CNS Drug Discovery (Discontinued), 9(2), 85-100.
100. Caulfield, M. P. (1993). Muscarinic receptors—characterization, coupling and function. Pharmacology & therapeutics, 58(3), 319-379.
101. Giessler, C., Dhein, S., Pönicke, K., & Brodde, O. E. (1999). Muscarinic receptors in the failing human heart. European journal of pharmacology, 375(1-3), 197-202.
102. DiFrancesco, D. (2010). The role of the funny current in pacemaker activity. Circulation research, 106(3), 434-446.
103. DiFrancesco, D., & Tortora, P. (1991). Direct activation of cardiac pacemaker channels by intracellular cyclic AMP. Nature, 351(6322), 145-147.
104. Logothetis, D. E., Kurachi, Y., Galper, J., Neer, E. J., & Clapham, D. E. (1987). The βγ subunits of GTP-binding proteins activate the muscarinic K+ channel in heart. Nature, 325(6102), 321-326.
105. Gurwitz, D., Haring, R., Heldman, E., Fraser, C. M., Manor, D., et al. (1994). Discrete activation of transduction pathways associated with acetylcholine m1 receptor by several muscarinic ligands. European Journal of Pharmacology: Molecular Pharmacology, 267(1), 21-31.
106. Gregory, K. J., Hall, N. E., Tobin, A. B., Sexton, P. M., & Christopoulos, A. (2010). Identification of orthosteric and allosteric site mutations in M2 muscarinic acetylcholine receptors that contribute to ligand-selective signaling bias. Journal of Biological Chemistry, 285(10), 7459-7474.
107. Nelson, C. D., Perry, S. J., Regier, D. S., Prescott, S. M., Topham, M. K., et al. (2007). Targeting of diacylglycerol degradation to M1 muscarinic receptors by ß-arrestins. Science, 315(5812), 663-666.
108. Pronin, A. N., Wang, Q., & Slepak, V. Z. (2017). Teaching an old drug new trick: agonism, antagonism, and biased signaling of pilocarpine through M3 muscarinic acetylcholine receptor. Molecular pharmacology, 92(5), 601-612.
109. Harada, M., Itoh, H., Nakagawa, O., Ogawa, Y., Miyamoto, Y., et al. (1997). Significance of ventricular myocytes and nonmyocytes interaction during cardiocyte hypertrophy: evidence for endothelin-1 as a paracrine hypertrophic factor from cardiac nonmyocytes. Circulation, 96(10), 3737-3744.
110. Dhaun, N., Goddard, J., Kohan, D. E., Pollock, D. M., Schiffrin, E. L., et al. (2008). Role of endothelin-1 in clinical hypertension: 20 years on. Hypertension, 52(3), 452-459.
111. Margulies, K. B., Hildebrand Jr, F. L., Lerman, A., Perrella, M. A., & Burnett Jr, J. C. (1990). Increased endothelin in experimental heart failure. Circulation, 82(6), 2226-2230.
112. Sakai, S., Miyauchi, T., Sakurai, T., Kasuya, Y., Ihara, M., et al. (1996). Endogenous endothelin-1 participates in the maintenance of cardiac function in rats with congestive heart failure: marked increase in endothelin-1 production in the failing heart. Circulation, 93(6), 1214-1222.
113. Schorlemmer, A., Matter, M. L., & Shohet, R. V. (2008). Cardioprotective signaling by endothelin. Trends in cardiovascular medicine, 18(7), 233-239.
114. Maguire, J. J., Kuc, R. E., Pell, V. R., Green, A., Brown, M., et al. (2012). Comparison of human ETA and ETB receptor signalling via G-protein and β-arrestin pathways. Life sciences, 91(13-14), 544-549.
115. Green, D. S., Rupasinghe, C., Warburton, R., Wilson, J. L., Sallum, C. O., et al. (2013). A cell permeable peptide targeting the intracellular loop 2 of endothelin B receptor reduces pulmonary hypertension in a hypoxic rat model. PLoS One, 8(11), e81309.
116. Sakai, S., Miyauchi, T., Kobayashi, M., Yamaguchi, I., Goto, K., et al. (1996). Inhibition of myocardial endothelin pathway improves long-term survival in heart failure. Nature, 384(6607), 353-355.
117. McMurray, J. J., Teerlink, J. R., Cotter, G., Bourge, R. C., Cleland, J. G., et al. (2007). Effects of tezosentan on symptoms and clinical outcomes in patients with acute heart failure: the VERITAS randomized controlled trials. Jama, 298(17), 2009-2019.
118. Anand, I., McMurray, J., Cohn, J. N., Konstam, M. A., Notter, T., et al. (2004). Long-term effects of darusentan on left-ventricular remodelling and clinical outcomes in the EndothelinA Receptor Antagonist Trial in Heart Failure (EARTH): randomised, double-blind, placebo-controlled trial. The Lancet, 364(9431), 347-354.
119. Wei, A., Gu, Z., Li, J., Liu, X., Wu, X., et al. (2016). Clinical adverse effects of endothelin receptor antagonists: insights from the meta-analysis of 4894 patients from 24 randomized double-blind placebo-controlled clinical trials. Journal of the American Heart Association, 5(11), e003896.
120. Shihoya, W., Nishizawa, T., Yamashita, K., Inoue, A., Hirata, K., et al. (2017). X-ray structures of endothelin ETB receptor bound to clinical antagonist bosentan and its analog. Nature Structural & Molecular Biology, 24(9), 758-764.
121. Brodde, O. E., & Michel, M. C. (1999). Adrenergic and muscarinic receptors in the human heart. Pharmacological reviews, 51(4), 651-690.
122. Mustafa, S. J., Morrison, R. R., Teng, B., & Pelleg, A. (2009). Adenosine receptors and the heart: role in regulation of coronary blood flow and cardiac electrophysiology (pp. 161-188). Springer Berlin Heidelberg.
123. Chuo, C. H., Devine, S. M., Scammells, P. J., Krum, H., Christopoulos, A., et al. (2016). VCP 746, a novel A1 adenosine receptor biased agonist, reduces hypertrophy in a rat neonatal cardiac myocyte model. Clinical and Experimental Pharmacology and Physiology, 43(10), 976-

982.
124. Welihinda, A. A., Kaur, M., Greene, K., Zhai, Y., & Amento, E. P. (2016). The adenosine metabolite inosine is a functional agonist of the adenosine A2A receptor with a unique signaling bias. Cellular signalling, 28(6), 552-560.
125. Donato, M., & Gelpi, R. J. (2003). Adenosine and cardioprotection during reperfusion–an overview. Molecular and cellular biochemistry, 251, 153-159.
126. Headrick, J. P., Hack, B., & Ashton, K. J. (2003). Acute adenosinergic cardioprotection in ischemic-reperfused hearts. American Journal of Physiology-Heart and Circulatory Physiology, 285(5), H1797-H1818.
127. Puhl, S. L., Kazakov, A., Müller, A., Fries, P., Wagner, D. R., et al. (2016). Adenosine A1 receptor activation attenuates cardiac hypertrophy and fibrosis in response to α1-adrenoceptor stimulation in vivo. British journal of pharmacology, 173(1), 88-102.
128. Müller, C. E., & Jacobson, K. A. (2011). Recent developments in adenosine receptor ligands and their potential as novel drugs. Biochimica et Biophysica Acta (BBA)-Biomembranes, 1808(5), 1290-1308.
129. Teerlink, J. R., Iragui, V. J., Mohr, J. P., Carson, P. E., Hauptman, P. J., et al. (2012). The safety of an adenosine A 1-receptor antagonist, rolofylline, in patients with acute heart failure and renal impairment: findings from PROTECT. Drug safety, 35, 233-244.
130. Gottlieb, S. S., Givertz, M. M., Metra, M., Gergich, K., Bird, S., et al. (2010). The effects of adenosine A1 receptor antagonism in patients with acute decompensated heart failure and worsening renal function: the REACH UP study. Journal of Cardiac Failure, 16(9), 714-719.
131. Wilbur, S. L., & Marchlinski, F. E. (1997). Adenosine as an antiarrhythmic agent. The American journal of cardiology, 79(12), 30-37.
132. Voors, A. A., Düngen, H. D., Senni, M., Nodari, S., Agostoni, P., et al. (2017). Safety and tolerability of neladenoson bialanate, a novel oral partial adenosine A1 receptor agonist, in patients with chronic heart failure. The Journal of Clinical Pharmacology, 57(4), 440-451.
133. Greene, S. J., Sabbah, H. N., Butler, J., Voors, A. A., Albrecht-Küpper, B. E., et al. (2016). Partial adenosine A1 receptor agonism: a potential new therapeutic strategy for heart failure. Heart failure reviews, 21, 95-102.
134. Tatemoto, K., Hosoya, M., Habata, Y., Fujii, R., Kakegawa, T., et al. (1998). Isolation and characterization of a novel endogenous peptide ligand for the human APJ receptor. Biochemical and biophysical research communications, 251(2), 471-476.
135. O'Dowd, B. F., Heiber, M., Chan, A., Heng, H. H., Tsui, L. C., et al. (1993). A human gene that shows identity with the gene encoding the angiotensin receptor is located on chromosome 11. Gene, 136(1-2), 355-360.
136. Hosoya, M., Kawamata, Y., Fukusumi, S., Fujii, R., Habata, Y.et al. (2000). Molecular and functional characteristics of APJ: tissue distribution of mRNA and interaction with the endogenous ligand apelin. Journal of Biological Chemistry, 275(28), 21061-21067.
137. Masri, B., Morin, N., Pedebernade, L., Knibiehler, B., & Audigier, Y. (2006). The apelin receptor is coupled to Gi1 or Gi2 protein and is differentially desensitized by apelin fragments. Journal of Biological Chemistry, 281(27), 18317-18326.
138. Szokodi, I., Tavi, P., Földes, G., Voutilainen-Myllylä, S., Ilves, M., et al. (2002). Apelin, the novel endogenous ligand of the orphan receptor APJ, regulates cardiac contractility. Circulation research, 91(5), 434-440.
139. Jia, Y. X., Lu, Z. F., Zhang, J., Pan, C. S., Yang, J. H., et al. (2007). Apelin activates L-arginine/nitric oxide synthase/nitric oxide pathway in rat aortas. Peptides, 28(10), 2023-2029.
140. Lee, D. K., Cheng, R., Nguyen, T., Fan, T., Kariyawasam, A. P., et al. (2000). Characterization of apelin, the ligand for the APJ receptor. Journal of neurochemistry, 74(1), 34-41.
141. Ishida, J., Hashimoto, T., Hashimoto, Y., Nishiwaki, S., Iguchi, T., et al. (2004). Regulatory roles for APJ, a seven-transmembrane receptor related to angiotensin-type 1 receptor in blood pressure in vivo. Journal of Biological Chemistry, 279(25), 26274-26279.
142. Cheng, X., Cheng, X. S., & Pang, C. C. (2003). Venous dilator effect of apelin, an endogenous peptide ligand for the orphan APJ receptor, in conscious rats. European journal of pharmacology, 470(3), 171-175.
143. Katugampola, S. D., Maguire, J. J., Matthewson, S. R., & Davenport, A. P. (2001). [125I] -(Pyr1) Apelin-13 is a novel radioligand for localizing the APJ orphan receptor in human and rat tissues with evidence for a vasoconstrictor role in man. British journal of pharmacology, 132(6), 1255-1260.
144. Scimia, M. C., Hurtado, C., Ray, S., Metzler, S., Wei, K., et al. (2012). APJ acts as a dual receptor in cardiac hypertrophy. Nature, 488(7411), 394-398.
145. Masri, B., Morin, N., Pedebernade, L., Knibiehler, B., & Audigier, Y. (2006). The apelin receptor is coupled to Gi1 or Gi2 protein and is differentially desensitized by apelin fragments. Journal of Biological Chemistry, 281(27), 18317-18326.
146. Földes, G., Horkay, F., Szokodi, I., Vuolteenaho, O., Ilves, M., et al. (2003). Circulating and cardiac levels of apelin, the novel ligand of the orphan receptor APJ, in patients with heart failure. Biochemical and biophysical research communications, 308(3), 480-485.
147. Chen, M. M., Ashley, E. A., Deng, D. X., Tsalenko, A., Deng, A., et al. (2003). Novel role for the potent endogenous inotrope apelin in human cardiac dysfunction. Circulation, 108(12), 1432-1439.
148. Kleinz, M. J., & Baxter, G. F. (2008). Apelin reduces myocardial reperfusion injury independently of PI3K/Akt and P70S6 kinase. Regulatory peptides, 146(1-3), 271-277.
149. Atluri, P., Morine, K. J., Liao, G. P., Panlilio, C. M., Berry, M. F., et al. (2007). Ischemic heart failure enhances endogenous myocardial apelin and APJ receptor expression. Cellular & molecular biology letters, 12, 127-138.
150. Sheikh, A. Y., Chun, H. J., Glassford, A. J., Kundu, R. K., Kutschka, I., et al. (2008). In vivo genetic profiling and cellular localization of apelin reveals a hypoxia-sensitive, endothelial-centered pathway activated in ischemic heart failure. American Journal of Physiology-Heart and

Circulatory Physiology, 294(1), H88-H98.
151. Charo, D. N., Ho, M., Fajardo, G., Kawana, M., Kundu, R. K., et al. (2009). Endogenous regulation of cardiovascular function by apelin-APJ. American Journal of Physiology-Heart and Circulatory Physiology, 297(5), H1904-H1913.
152. Kuba, K., Zhang, L., Imai, Y., Arab, S., Chen, M., et al. (2007). Impaired heart contractility in Apelin gene–deficient mice associated with aging and pressure overload. Circulation research, 101(4), e32-e42.
153. Wang, W., McKinnie, S. M., Patel, V. B., Haddad, G., Wang, Z., et al. (2013). Loss of Apelin exacerbates myocardial infarction adverse remodeling and ischemia-reperfusion injury: therapeutic potential of synthetic Apelin analogues. Journal of the American Heart Association, 2(4), e000249.
154. Hakak, Y., Shrestha, D., Goegel, M. C., Behan, D. P., & Chalmers, D. T. (2003). Global analysis of G-protein-coupled receptor signaling in human tissues. FEBS letters, 550(1-3), 11-17.
155. Nebigil, C. G., Jaffré, F., Messaddeq, N., Hickel, P., Monassier, L., et al. (2003). Overexpression of the serotonin 5-HT2B receptor in heart leads to abnormal mitochondrial function and cardiac hypertrophy. Circulation, 107(25), 3223-3229.
156. Shyu, K. G. (2009). Serotonin 5-HT2B receptor in cardiac fibroblast contributes to cardiac hypertrophy: a new therapeutic target for heart failure. Circulation research, 104(1), 1-3.
157. Kim, J., Ogai, A., Nakatani, S., Hashimura, K., Kanzaki, H., et al. (2006). Impact of blockade of histamine H2Receptors on chronic heart failure revealed by retrospective and prospective randomized studies. Journal of the American College of Cardiology, 48(7), 1378-1384.
158. Devarakonda, T., & Salloum, F. N. (2018). Heart disease and relaxin: new actions for an old hormone. Trends in Endocrinology & Metabolism, 29(5), 338-348.
159. Morooka, H., Iwanaga, Y., Tamaki, Y., Takase, T., Akahoshi, Y., et al. (2012). Chronic administration of oral vasopressin type 2 receptor antagonist tolvaptan exerts both myocardial and renal protective effects in rats with hypertensive heart failure. Circulation: Heart Failure, 5(4), 484-492.
160. Means, C. K., & Brown, J. H. (2009). Sphingosine-1-phosphate receptor signalling in the heart. Cardiovascular research, 82(2), 193-200.