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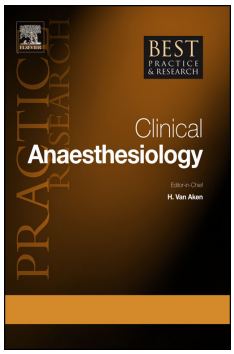

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D. Wong, P.N.W. Tsai, K.Y. Ip, M.G. Irwin

PII: S1521-6896(18)30072-7

DOI: 10.1016/j.bpa.2018.06.013

Reference: YBEAN 996

To appear in: *Best Practice & Research Clinical Anaesthesiology*

Received Date: 28 June 2018

Accepted Date: 29 June 2018

Please cite this article as: Wong D, Tsai PNW, Ip KY, Irwin MG, New antihypertensive medications and clinical implications, *Best Practice & Research Clinical Anaesthesiology* (2018), doi: 10.1016/j.bpa.2018.06.013.

Review article

New antihypertensive medications and clinical implications

D. Wong, [1] P. N. W. Tsai,[2] K. Y. Ip, [3] and M. G. Irwin[4]

1 BSc, MBBS(London), MRCA. Resident, Department of Anaesthesiology, Queen Mary Hospital, Hong Kong Special Administrative Region, China

drdonovanwong@gmail.com

2 MBBS(HK), MRCP(UK), FHKAM. Associate Consultant, Adult Intensive Care Unit, Queen Mary Hospital, Hong Kong Special Administrative Region, China

nwtsai@hku.hk

3 MBChB(CUHK), MRCP(UK), FHKAM. Associate Consultant, Department of Anaesthesiology, Queen Mary Hospital, Hong Kong Special Administrative Region, China

ipkamyuen@gmail.com

4 MBChB(Glasg), MD, FRCA, FANZCA, FHKAM. Professor and Head, Department of Anaesthesiology, The University of Hong Kong, Hong Kong Special Administrative Region, China

mgirwin@hku.hk

Correspondence to: M. G. Irwin

Email: mgirwin@hku.hk

Abstract

Hypertension remains a global public health issue and is a leading preventable risk factor for many causes of mortality and morbidity. Although it is generally managed as an outpatient chronic disease, anaesthetists will inevitably encounter patients with hypertension, ranging from undiagnosed asymptomatic to chronic forms with end organ damage(s). An understanding of perioperative management of anti-hypertensive pharmacotherapy is crucial. While many drugs will be familiar, new drug groups have evolved in recent years, which has relevance for blood pressure control and perioperative care.

This article also describes new antihypertensive agents currently available or under development that could impact perioperative management.

Keywords: pre-operative factors; hypertension; perioperative management; novel antihypertensives

Introduction

Hypertension is a growing global public health issue and was estimated to affect 1.13 billion people worldwide in 2015 [1]. Due to increasing longevity and advances in surgical and anaesthetic techniques, older patients are presenting for surgery and anaesthetists face more hypertensive patients requiring major operations. Hypertension is the leading risk factor for deaths due to cardiovascular disease, chronic renal diseases and cerebrovascular disease [2, 3]. In untreated cases, it is associated with cardiovascular risk and the onset of vascular and kidney injury. Concerning perioperative care, poorly controlled hypertension can lead to cancellation or postponement of surgery [4]. This is reflected in the latest Guidelines from the American College of Cardiology and the American Heart Association (ACC/ AHA) that deferring surgery may be considered in patients with planned elective major operations if the systolic blood pressure (SBP) reads ≥180mmHg or the diastolic blood pressure (DBP) is ≥110mmHg [5]. In particular, patients with a preoperative DBP of ≥110mmHg have been shown to be at increased risk of cardiovascular complications and renal failure [6]. There is one study showing that poorly controlled hypertension led to labile intraoperative blood pressure (BP), although it failed to show an association with 30-day mortality [7]. There is, however, growing evidence associating intraoperative hypotension with postoperative mortality, myocardial injury and renal failure in patients undergoing non-cardiac surgery [8-12].

Definition of hypertension

Hypertension was previously defined as SBP of ≥140mmHg or DBP of ≥90mmHg [13-15]. Recently, there has been a proliferation of hypertension guidelines, including the Eighth Report of the Joint National Committee (JNC 8) [16] and the 2017 ACC/ AHA guidelines [5]. These have given rise to a paradigm shift with seemingly “tighter” BP targets. The ACC/

AHA guidelines are most notable for redefining hypertension as SBP of ≥130mmHg or DBP of ≥80mmHg for anyone at cardiovascular risk [5]. The SPRINT trial [17] is the cornerstone of the pertinent changes. It compared two thresholds of antihypertensive therapy in patients at high cardiovascular risk without diabetes and concluded that aiming for a reduction of SBP to less than 120 mmHg, as compared with less than 140 mmHg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause, but it was at the expense of higher rates of renal failure, electrolyte abnormality and syncope. The SPRINT trial received a number of criticisms concerning its study design and applicability in the real world [18]. No significant benefit in cardiovascular or cerebrovascular outcome was found in other study populations which used the same or similar BP targets as SPRINT [19, 20]. Table 1 summarises the recommendations from existing guidelines.

There is no universally accepted "magic number" for BP target, and multiple confounding factors have been identified. White-coat (overestimation of BP) and masked hypertension (underestimation of BP) [21] are phenomena that can lead to inaccurate assessment, which often happens in the clinic setting. Table 2 summarises the BP patterns in various circumstances. Theoretically, use of out-of-office monitoring can provide a better and more accurate appreciation of BP control, yet few data regarding its utility has been reported. The utilisation of ambulatory blood pressure monitoring by anaesthetists in the pre-assessment clinic setting has been investigated and potentially has a role in reducing inappropriate postponement of elective surgery secondary to hypertension [22]. The condition is further complicated by biological rhythms and circadian changes of patients [23]. Finally, to address anaesthetist's concern, a recent cohort study reported that pre-induction mean arterial pressure (MAP) was higher than the preoperative MAP, probably because of psychological stress [24]. This spurious BP rise makes perioperative BP targeting even more challenging to be achieved.

Personalisation

It has been reported that each 5 mmHg reduction in SBP or 2 mmHg reduction in DBP can result in a significant reduction in cardiovascular morbidity and mortality [25]. However, current evidence suggests that hypertension itself should not be treated alone but include assessment of all cardiovascular risk factors. Personalisation is an emerging concept to be noted, taking into account an individual's baseline blood pressure [26] and cardiovascular disease risks [5], which is especially crucial in perioperative blood pressure management. A recent large, retrospective, cohort study investigated the relationship between intraoperative hypotension, using an absolute intraoperative MAP and relative MAP thresholds, and postoperative acute kidney and myocardial injury. It concluded that a strategy aiming at maintaining MAP above 65 mmHg appeared to be as good as one based on relative reduction thresholds of 20% [11]. However, if the underlying pathophysiology and autoregulation are taken into account, hypertensive patients may have a lower limit of autoregulation and require a higher MAP target [27]. Secondly, an individual's underlying cardiovascular disease (CVD) risk in terms of 10-year risk of atherosclerotic CVD (ASCVD) should be calculated (http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/) and incorporated into the blood pressure recommendation [5]. For instance, if the risk of CVD is more than 10% over ten years, a tighter blood pressure of 130/80 mmHg or less is recommended based on the latest ACC/ AHA guidelines. The 2014 guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery [28] also recommends perioperative beta-blocker use based on a Revised Cardiac Risk index (Table 3) [29].

Intraoperative hypotension versus preoperative hypertension, why bother?

The management of chronic medications including antihypertensives during the perioperative period poses significant challenges. The problem is twofold. Firstly, polypharmacy is an issue. One study showed at least half of surgical patients were prescribed chronic medications (on average nine different drugs) prior to surgery, and one-fifth of the drugs were released within the last ten years [30]. The study also showed that taking a drug unrelated to surgery was associated with an increased relative risk of a postoperative complication of 2.7; on the contrary, unnecessary withholding of the usual medications in the postoperative period may result in nonsurgical complications, e.g. cardiac events. Secondly, the world's population is ageing, and it is estimated that by 2050 about 16% of the world's population will be aged over 65 years [31]. A different focus on the perceived risk and preoperative evaluation is required.

It should be the intraoperative hypotension and BP lability, rather than hypertension per se, that raises concerns for anaesthetists. Previous studies have demonstrated intraoperative hypotension and lability of blood pressure can jeopardise organ perfusion and is associated with postoperative mortality and morbidity [8-12], which can be further complicated by advanced age, poorly controlled blood pressure and antihypertensive medication side effects. However, "baseline" blood pressure varies among individuals and the concept of intraoperative hypotension is poorly defined [32]. Several definitions including a SBP below 80 mmHg, a decrease of SBP more than 20% below baseline, or combinations of absolute and relative SBP thresholds have been used [32]. Researchers have pioneered the use of prediction tools and surrogate markers to predict the occurrence of undesirable events. For instance, the use of preoperative cardiac troponin I [33] and perioperative natriuretic peptide levels [34] has been used in predicting postoperative 30-day mortality and major adverse cardiac events after major surgeries. Likewise, research has been conducted to predict the occurrence of intraoperative hypotension and BP lability. Preoperative functional capacity

[35], vascular volume status [35, 36] and coagulation profile [37] have been studied in selected groups of patients to predict intraoperative hypotension. Recently, Cheung et al [38] postulated a scoring system (the "HEART" score) which identified 5 items including preoperative Heart rate (<60 beats/min), preoperative hypotension (<110/60 mm Hg), old age (Elderly > 65 years), preoperative renin-Angiotensin blockade (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or beta-blockers), Revised cardiac risk index (≥3 points) and Type of surgery (major surgery). Each risk factor scored one point, and the study showed each 1-point increment was associated with an odds ratio of 2.51 (95% confidence interval, 1.79-3.53) for intraoperative hypotension or bradycardia. Lately, the HYPE trial, a prospective, randomised, controlled trial investigating the use of a "Hypotension Probability Indicator" algorithm for prediction of intraoperative hypotension, has commenced (www.ClinicalTrials.gov: NCT03376347). To date, there is no consensus on predictive assessment and further clinical validation and outcome studies are warranted before any recommendation on the utility can be made.

Latest evidence on the perioperative management of antihypertensives

For patients with SBP of <180mmHg and DBP of <110mmHg, current evidence suggests that it is not an independent risk factor for perioperative complications, and no evidence supports delaying surgery in the absence of target organ damage [39]. However, in patients with poorly controlled hypertension (SBP of ≥180mmHg or DBP of ≥110mmHg) undergoing planned elective major surgery, surgery should be deferred if possible until BP can be controlled [5], yet it is not known if the risk of cardiovascular complications can be reduced. As a general rule, it is reasonable to continue chronic medications for hypertension until surgery [5]. Abrupt cessation of beta-blockers and clonidine can lead to withdrawal syndromes and, paradoxically, cause sympathetic overactivity and acute hypertension [40].

Intraoperative BP lability appears more prominent in patients with poorly controlled BP, with an exaggerated surge in BP and heart rate noted during induction of anaesthesia [6]. Selected groups of antihypertensives will be discussed below.

Beta-blockers

Patients on chronic treatment with beta-blockers due to ischemic heart disease, arrhythmias or hypertension should be maintained on the medication throughout the perioperative period [5]. Patients taking the medication chronically for management of angina and ischemic heart disease are at particular risk of ischemia with beta-blocker withdrawal.

For beta-blocker naïve patients, the initiation of beta-blockade purely for perioperative reasons is no longer routinely recommended. Theoretically, beta-blockers offer possible benefit in prevention of perioperative cardiac events. However, the POISE (PeriOperative ISchemic Evaluation) trial in 2008 showed that they should not be started on the day of surgery in light of a potential paradoxical increase in the risk of stroke, bradycardia and death [41]. The trial received criticism for the choice of medication, dosage and timing of initiation, which led to more hypotensive episodes and a higher incidence of stroke in the study population. The DECREASE-IV trial in 2009 reported among patients at intermediate risk undergoing non-cardiovascular surgery, the preoperative use of bisoprolol for a median of 34 days was associated with a significant reduction in 30-day cardiac death and nonfatal myocardial infarction (2.1% versus 6.0%, $p = 0.002$), yet no difference in the incidence of stroke was reported [42]. In selected patient populations including those with known ischaemic heart disease or undergoing high-risk surgery with presence of clinical risk factors [28, 43], initiation and dose titration of beta-blockers over a period of time is suggested in view of the heterogeneous response due to pharmacogenetic variability [44].

Angiotensin-Converting Enzyme Inhibitors/ Angiotensin II Receptor Blockers (ACEIs/ ARBs)

Perioperative continuation of ACEIs/ ARBs has been controversial because of fear of intraoperative hypotension [45]. In the absence of heart failure or left ventricular dysfunction, it is reasonable to withhold the agents prior to surgery [5]. A recent prospective, cohort study investigated the practice of withholding these drugs before major noncardiac surgery and demonstrated a lower risk of primary composite outcome (all-cause death, stroke, or myocardial injury (adjusted relative risk, 0.82%; 95% CI, 0.70 to 0.96; P = 0.01)) and less intraoperative hypotension (adjusted relative risk, 0.80%; 95% CI, 0.72 to 0.93; P <0.001) [46]. On the other hand, timely reinstitution is advised as soon as possible after surgery, as withholding them for more than two days after surgery has been associated with increased 30-day mortality [47, 48].

Others

Patients on chronic treatment with calcium channel blockers and nitroglycerin due to ischemic heart disease, arrhythmias or hypertension should be maintained on the medication throughout the perioperative period. There is scant evidence to support the initiation preoperatively for theoretical “cardioprotection” in non-cardiac surgery [49, 50].

No consensus exists concerning the perioperative management of chronic diuretic use [51, 52], but the conventional practice is to withhold diuretics on the morning before surgery. For patients on diuretics perioperatively, volume status and electrolyte balance are a concern, as hypokalaemia can theoretically increase the risk of perioperative arrhythmia and hypovolaemia can lead to significant intraoperative hypotension after systemic vasodilatation induced by anaesthetic agents.

Challenges - New antihypertensive agents

Apart from the "ABCD" of commonly prescribed antihypertensive medications (i.e. A= ACEIs/ ARBs; B= Beta-blockers; C= Calcium channel blockers; D= Diuretics), there are a plethora of newly developed antihypertensives which act on different pathways (Tables 4 and 5). The diagnosis of resistant hypertension is made when a patient is taking at least three antihypertensives of different classes, including a diuretic, at optimal doses but is still unable to achieve control, or is requiring four or more medications to achieve BP control [53]. 10% to 15% of the hypertensive population has resistant hypertension, and it is estimated to be 4% higher with the newly recommended 2017 ACC/ AHA guidelines [5]. Apart from drug nonadherence, intolerance to existing antihypertensive medications is also one of the contributing factors, which has led to the development of novel drug classes (Figures 1 and 2). The common ones are addressed below.

Centrally acting agents

Clonidine, a centrally acting alpha-2 agonist, stimulates the locus ceruleus and brainstem receptors resulting in a reduction in sympathetic outflow from the central nervous system by restricting the release of norepinephrine. The decrease in plasma norepinephrine concentrations leads to hypotension. Clonidine has been widely used in anaesthesia for analgesia, antiemesis, anxiolysis, sedation, haemodynamic stability and myocardial protection. As an antihypertensive, patients on chronic treatment with clonidine for BP control should be maintained on the medication throughout the perioperative period given possible rebound hypertension following abrupt withdrawal [40, 54].

Anecdotal studies suggested that preoperative initiation of clonidine may be associated with improved perioperative outcomes [55, 56]; however, more recent research has been contradictory. The POISE-2 trial [57] suggested that preoperative initiation of clonidine did

not reduce the rate of death or nonfatal myocardial infarction but increased the rate of nonfatal cardiac arrest and hypotension. A sub-study of the POISE-2 trial also found no reduction in the risk of acute kidney injury (alpha-2 agonists have been suggested to have renal and neuroprotective effects) [58]. Based on current evidence, clonidine should not be initiated preoperatively for possible cardioprotection [59].

Renin inhibitors

The renin-angiotensin-aldosterone system (RAAS) regulates the hemodynamic balance and is a crucial element in hypertension. Hypertensive patients tend to have excessive RAAS activity [60, 61]. Interruption of the system at different levels is one of the targets for antihypertensive use (Figure 1). RAAS inhibitors, including ACEIs and ARBs, have been widely used in the management of hypertension. There is, however, a phenomenon called "RAAS escape" [62], where existing drugs fail to block RAAS activity entirely with increasing concentrations of renin. Aliskiren is the only direct and selective renin inhibitor currently available for the treatment of hypertension, having no effect on (pro)renin binding to the receptors, but blocking the site for renin activation. It leads to a reduction in plasma renin activity (PRA), which seems to induce cardiorenal protection in animal studies [63]. However, no large randomised clinical trials have, so far, demonstrated a beneficial effect on this. The AQUARIUS trial [64] concluded the use of aliskiren therapy versus placebo did not result in improvement or slowing of progression of coronary atherosclerosis. The APPOLO trial [65] compared the use of aliskiren alone or with other antihypertensives in the elderly with SBP <160mmHg; it was terminated prematurely by the sponsor, but no harm was seen in the aliskiren treated group.

On the other hand, aliskiren combination therapy has been shown to be associated with adverse events including hyperkalaemia, hypotension and renal failure, especially in

susceptible populations, e.g. patients with heart failure, diabetes and underlying kidney disease. The ATTITUDE trial [66] investigated the addition of aliskiren to standard therapy with renin-angiotensin system (RAS) blockade in patients with type 2 diabetes and was stopped prematurely due to an undesirable risk / benefit ratio, which showed no cardiovascular or renal protection, but a trend towards adverse effects including cardiovascular deaths (5.8% vs. 5.0%), stroke (3.4% vs. 2.8%) and end-stage renal disease (2.8% vs. 2.6%). The ASTRONAUT trial [67] investigated the addition of aliskiren to standard heart failure therapy in patients with a reduced left ventricular ejection fraction and concluded that the initiation of aliskiren did not reduce cardiovascular death or heart failure rehospitalisation at six or twelve months, but resulted in higher rates of hyperkalaemia, hypotension and renal failure. The ATMOSPHERE trial [68] concluded that the addition of aliskiren to enalapril in patients with heart failure showed no added benefit but more adverse events in terms of hypotensive symptoms, hyperkalaemia and renal impairment.

It is apparent that patient outcomes do not improve when adding aliskiren to other agents that block the RAAS. This concurs with the latest ACC/ AHA guidelines suggestion that simultaneous use of an ACE inhibitor, ARB, and/or renin inhibitor is potentially harmful and is not recommended to treat adults with hypertension [5]. There is no existing guideline on perioperative management of aliskiren. As the therapeutic and side effect profiles are similar to ACEIs/ ARBs, it is reasonable to follow the same approach until more data are available.

Vasopeptidase inhibitors

Neprilysin (neutral endopeptidase 24.11) is an enzyme responsible for the breakdown of natriuretic peptides and has been a therapeutic target for hypertension and other cardiovascular diseases [69, 70]. Inhibition of neutral endopeptidase (NEP) increases the level of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type

natriuretic peptide (CNP). The natriuretic peptides act as endogenous inhibitors of the renin-angiotensin system, and the increase in circulating natriuretic peptide levels can lead to natriuresis, vasodilatation, renin-angiotensin-aldosterone system inhibition and reduced sympathetic drive (Figure 2). However, apart from catalysing the degradation of vasodilator peptides and bradykinin, neprilysin also degrades the vasoconstrictor peptides including angiotensin II and endothelin-1 [71, 72]. It explains why pure neprilysin inhibitor monotherapy was not found to be beneficial in patients with heart failure [73] and may even have led to increased blood pressure in normotensives [74].

Strategies to inhibit both neprilysin and the RAAS system have been implemented. A combination of neprilysin and ACEI was shown to evoke greater antihypertensive effects [75] and clinical efficacy [76] but was associated with an unacceptably high rate of angioedema [75], likely attributable to raised bradykinin levels [77].

On the contrary, the combination of neprilysin inhibitors with ARBs that block type 1 angiotensin II (AT_1) receptors does not exhibit bradykinin metabolism inhibition and, hence, the associated angioedema effect. This new class of pharmacological agents is termed "angiotensin receptor- neprilysin inhibitor (ARNI)". Sacubitril-valsartan, also known as LCZ696, is the first compound in this class, and has shown encouraging results in initial clinical trials [78, 79].

There is growing evidence on the use of LCZ696 in patients with hypertension and heart failure. The PARAMOUNT trial [80] examined its effect on biomarkers in patients with heart failure and preserved ejection fraction. It showed a reduction in N-terminal pro-B-type natriuretic peptide, a marker of left ventricular wall stress. No additional risk of angioedema or other adverse effects were noted. The PARADIGM-HF trial [81, 82] demonstrated that LCZ696 was superior to enalapril in patients with heart failure with reduced ejection fraction, in reducing the risk of cardiovascular death and hospitalisation for heart failure by 21%

(P<0.001) and decreasing the symptoms and physical limitations of heart failure (P=0.001). The LCZ696 group was not found to have an increased risk of severe angioedema.

The PARAMETER study [83] demonstrated the superiority of LCZ696 in elderly patients with systolic hypertension regarding blood pressure control. Again, no life-threatening angioedema was reported in the LCZ696 group.

The European Association for Cardio-Thoracic Surgery guidelines in 2017 recommended the use of LCZ696 as a replacement for an ACEI in ambulatory patients with reduced LVEF (<40%) who remain symptomatic despite optimal treatment with an ACEI, beta-blocker and aldosterone antagonists [84]. However, there is no consensus on the perioperative management of neprilysin inhibitors at present and clinical data remain scanty, but a general principle applies to perioperative care. Firstly, neprilysin inhibitors act on two enzymes that inactivate bradykinin, i.e. angiotensin-converting enzyme and neprilysin, which can increase the risk of angioedema. Perioperatively, this raises the concern of life-threatening angioedema, airway problems and, hence, the recommendation to avoid the concomitant use of neprilysin inhibitors and ACEIs in the perioperative setting. If angioedema occurs, immediate discontinuation and appropriate treatment are suggested. Secondly, renal function, electrolyte levels and volume status should be monitored as for any other RAAS blocker. Concomitant use with potassium-sparing diuretics may lead to an increase in serum potassium concentrations, and postoperative use of non-steroidal anti-inflammatory drugs in the elderly population may worsen renal function [85].

Future approaches

There has been a surge of research on antihypertensives with different potential putative therapeutic targets including neurohormonal modulation (including renin-angiotensin, aldosterone and vasopressin), vaccination [86], microbiota regulation [87] and interventional

treatment (including renal denervation [88] and baroreflex activation therapy [89]). These are fascinating and may well have a future therapeutic role but are beyond the scope of this paper.

Summary

Patients with hypertension pose unique challenges for anaesthesia and perioperative care. There is still much debate on the optimal perioperative management and anaesthetists are facing more complex clinical decisions on managing different antihypertensives. A better knowledge of the drug targets, the sites of action, pharmacogenetic variability and the potential drug-drug interactions allow anaesthetists to optimise perioperative anaesthetic management and normotension. “One-size-fits-all” management does not exist; and personalised risk stratification, prediction and prevention of adverse effects is essential.

Practice points

- Hypertension is a major public health issue and is the leading preventable cause of death worldwide
- Patients with poorly controlled hypertension are at increased risk of perioperative complications
- An understanding of mechanisms of action and pharmacologic properties of various antihypertensive drugs is essential in perioperative management
- Novel antihypertensives create unique challenges to anaesthetists in perioperative decision making
- Personalisation and “stratified” approach of perioperative care is the key to success

Research agenda

- Algorithm for preoperative prediction and early identification of perioperative complications and intraoperative hemodynamic compromise.
- Determination of the optimal strategy for management of newer antihypertensive drugs.
- Investigate the target-organ protection effects of novel antihypertensive drugs.

Financial support

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

LKKL, PNWT, KYI no competing interests declared. MGI is an editor of a number of journals including Anaesthesia, Expert Opinion in Pharmacotherapy and Perioperative Medicine.

Acknowledgments

None.

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Tables

Table 1: Blood pressure targets and recommendations

Source	Recommended Threshold for Hypertension Diagnosis	Recommended Treatment Goals
NICE/BHS CG127 2011[90]	140mmHg Systolic/ 90mmHg Diastolic	<140/90mmHg in patients aged < 80 years <150/90mmHg in patients aged ≥ 80 years
ESC/ ESH 2013[15]	140/90mmHg	<140/90mmHg
AHA/ ACC 2014[14]	140/90mmHg	<140/90mmHg
JNC-8 2014[16]	140/90 mmHg for patients <60 years old; 150/90 mmHg for patients ≥60 years old	<140/90mmHg in patients aged <60 years old <150/90mmHg in patients aged ≥60 years old <140/90mmHg in adult patients with chronic kidney disease or diabetes
Heart Foundation 2016[91]	140/90mmHg	<140/90mmHg in patients aged <75 years old <120mmHg systolic in patients aged ≥75 years old or selected high cardiovascular risk populations with close follow-up <140/90mmHg in adult patients with chronic kidney disease or diabetes
AHA/ ACC 2017[5]	130/80mmHg	<130/80mmHg in patients aged <65 years old <130mmHg systolic in patients aged ≥65 years

	old non-institutionalised ambulatory community-dwelling adults
	<130/80mmHg in adult patients with chronic kidney disease or diabetes

*NICE/ BHS= National Institute for Health and Care Excellence/ British Hypertension Society; AHA/ ACC= American College of Cardiology/ American Heart Association; ESC/ESH= European Society of Cardiology/ European Society of Hypertension; JNC-8= Eighth Joint National Committee

† Individual with systolic BP and diastolic BP in 2 categories should be designated to the higher BP category. BP = blood pressure.

Table 2: Blood pressure patterns and the influence of circumstance [5]

	Office/ Clinic/ Healthcare Setting	Home/ Nonhealthcare/ ABPM Setting
Normotensive	⇔	⇔
Sustained hypertension	⇑	⇑
Masked hypertension	⇔	⇑
White coat hypertension	⇑	⇔

***** ⇔ = No hypertension; ⇑ = hypertension; ABPM= ambulatory blood pressure monitoring

Table 3: Revised Cardiac Risk Index [29]

Risk factor	Points
Cerebrovascular disease	1
Congestive heart failure	1
Creatinine level > 2.0 $mg.dL^{-1}$	1
Diabetes mellitus requiring insulin	1
Ischemic cardiac disease	1
Supra-inguinal vascular surgery, intrathoracic surgery, or intra-abdominal surgery	1
Risk of major cardiac event	
Points	Risk % (95% confidence interval)
0	0.4 (0.05-1.5)
1	0.9 (0.3-2.1)
2	6.6 (3.9-10.3)
$\geq$3	$\geq$11 (5.8-18.4)

Table 4: Commonly used antihypertensive drugs

Pharmacological classes	Sub-classes	Drugs
Major classes		
ACEIs		benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril
ARBs		azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan
Beta-blockers	Non-vasodilating with β 1- selectivity	acebutolol, atenolol, betaxolol, bisoprolol
	Non-vasodilating without β 1-selectivity	carteolol, esmolol, metoprolol, nadolol, oxprenolol, penbutolol, propranolol, timolol
	Vasodilating	celiprolol, carvedilol, labetolol, nebivolol, pindolol
CCBs	Non-dihydropyridines	diltiazem, verapamil
	Dihydropyridines	amlodipine, felodpine, isradipine, nicardipine, nifedipine, nisoldipine
Diuretics	Loop diuretics	bumetanide, furosemide, torsemide
	Thiazide diuretics	chlorthalidone, hydrochlorothiazide, indapamide, metolazone
	Potassium sparing	amiloride, triamterene, spironolactone,

	diuretics	eplerenone
Alpha blocker	Higher affinity for α1 receptor	phenoxybenzamine
Other classes		
Centrally acting agents		clonidine, methyldopa, rilmenidine
Renin inhibitors		aliskiren
Neprilysin inhibitors	(combination with an RAS blocker or an endothelin converting enzyme)	

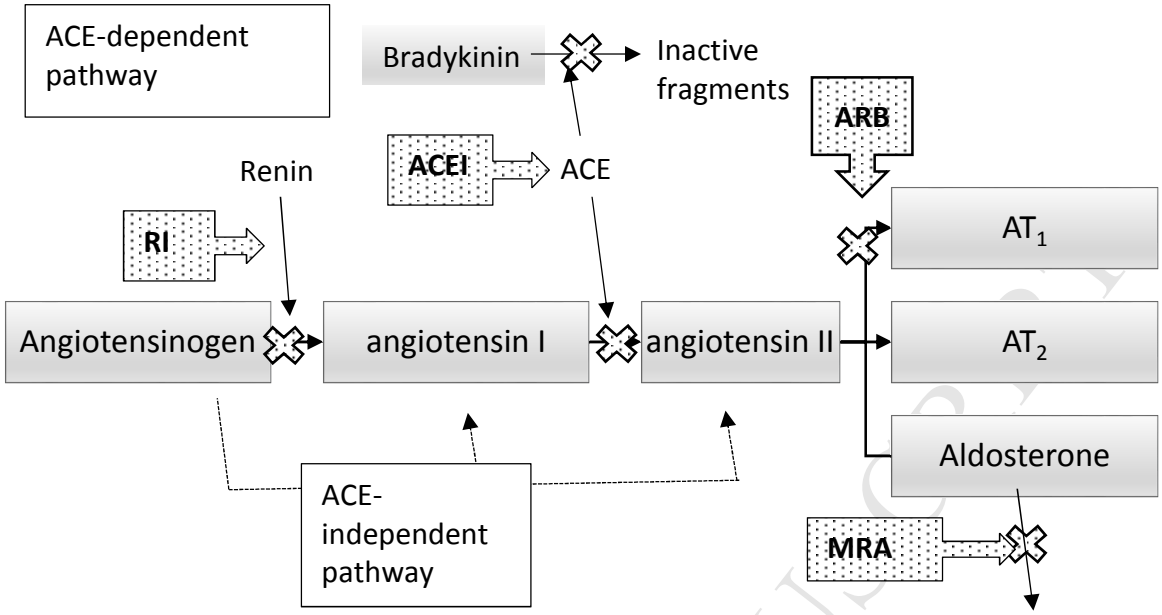
*ACEI= angiotensin-converting enzyme inhibitor; ARB= angiotensin II receptor blocker; CCB= calcium channel blocker; RAS= renin angiotensin system; β= beta; = alpha;

Table 5: Selected novel drugs for hypertension

Mechanism of Action	Drug	Status
Mineralocorticoid receptor antagonist	BAY 94-8862 (Finerenone)	Phase IIb
Aldosterone synthase inhibitor	LCI699	Stopped at Phase II
Dual acting endothelin-converting enzyme-neprilysin inhibitor	SLV-306 (Daglutril)	Phase II
AT2 receptor agonist	Compound 21	Preclinical
ACE2 activator	rhACE2	Phase II
Nitric oxide-donor	BAY-63-2521 (Riociguat)	Phase IV
Soluble epoxide hydrolase inhibitors	AR9281	Stopped at Phase II
Dopamine beta-hydroxylase inhibitor	BIA 5-453 (Etamicastat)	Phase I
Vaccines		
Vaccine against angiotensin II	CYT006-AngQβ	Phase II
Vaccine against angiotensin II type 1 receptor	ATRQβ -001	Preclinical
Vaccine against angiotensin I/II	Anti-angiotensin peptide	Preclinical

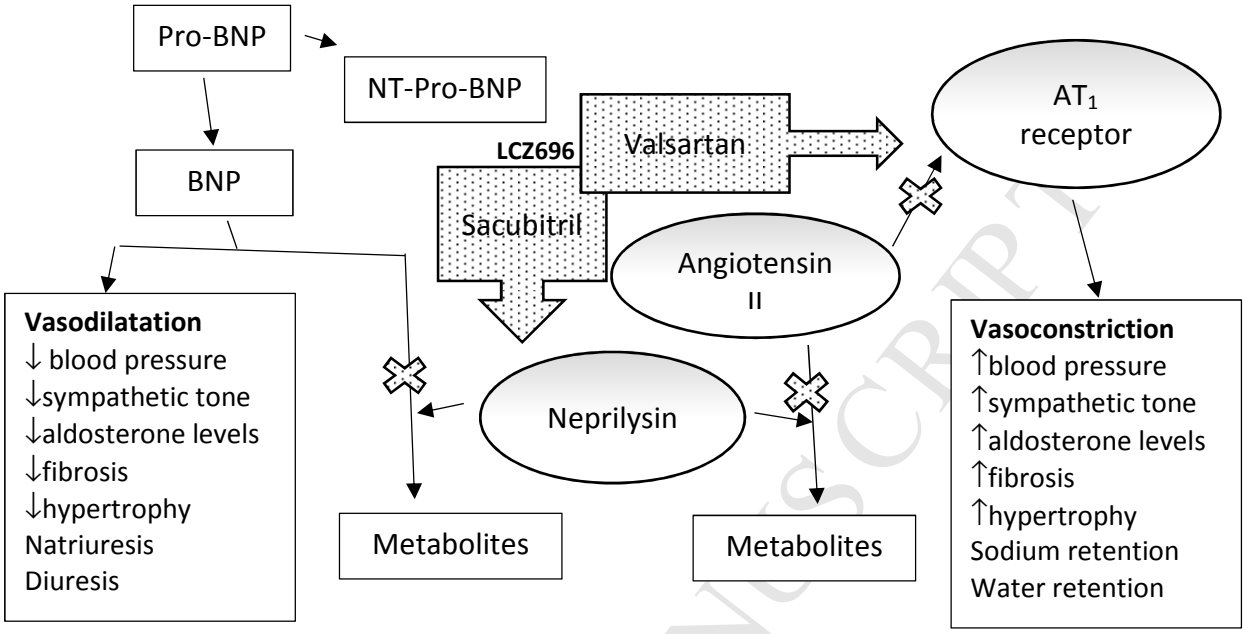
*AT2= angiotensin II type 2; ACE2= angiotensin-converting enzyme 2; rhACE2= recombinant human ACE2;

Figure 1: Simplified schematic of the RAAS system



*RAAS= renin-angiotensin-aldosterone system; RI= renin inhibitor; ACE= angiotensin-converting enzyme; ACEI= angiotensin-converting enzyme inhibitor; ARB= angiotensin II receptor blocker; AT_1= angiotensin II receptor type 1; AT_2= angiotensin II receptor type 2; MRA= mineralocorticoid receptor antagonist

Figure 2: Dual acting angiotensin receptor-neprilysin inhibitors



*BNP= brain natriuretic peptide; NT-pro-BNP= N-terminal pro brain natriuretic peptide; AT_1= angiotensin II receptor type 1