HYPERTENSION DRUG TREATMENT

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Clinical Practice Guidelines

2020 International Society of Hypertension Global Hypertension Practice Guidelines

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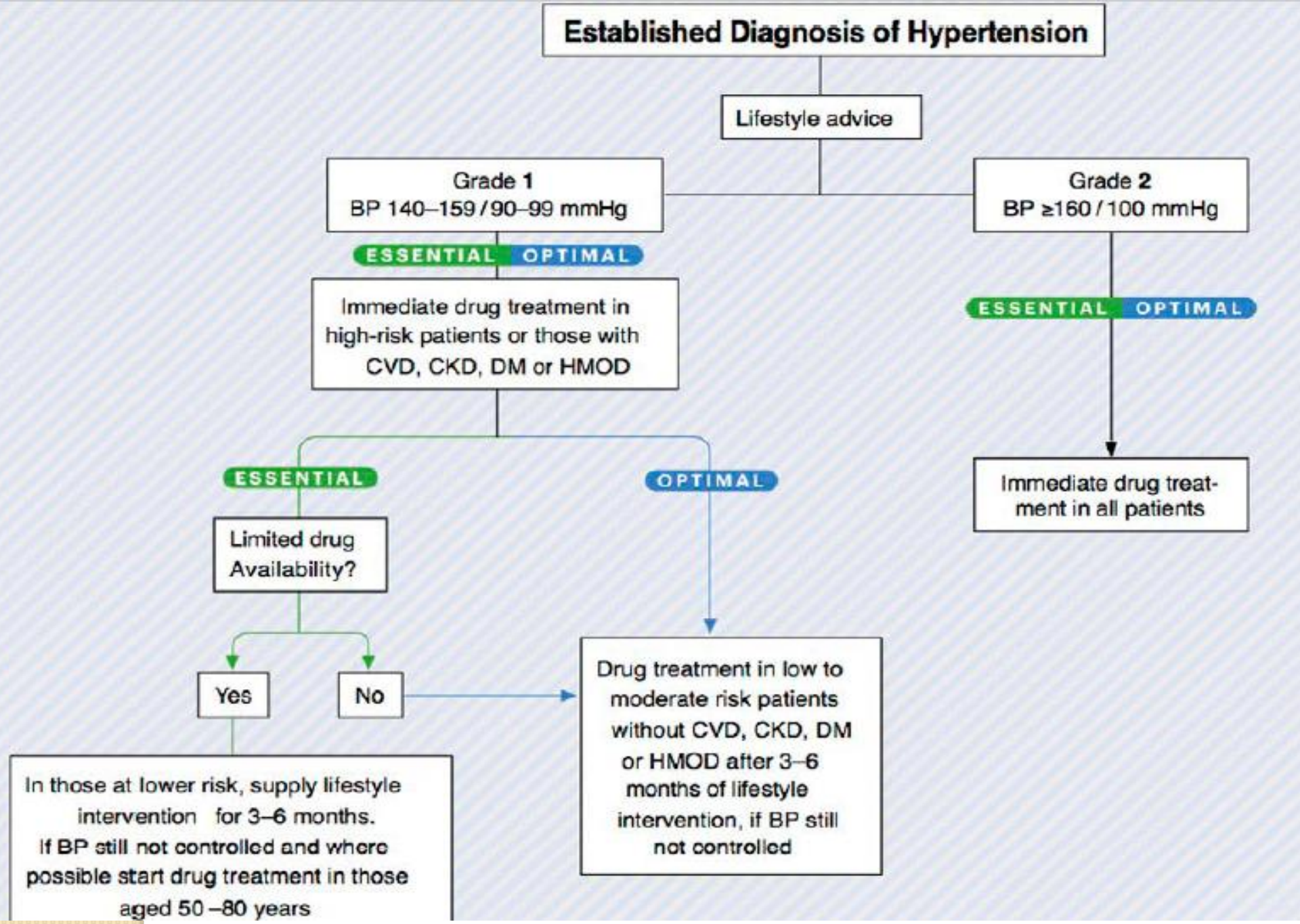
***Hypertension* June 2020**

Table 9. Ideal Characteristics of Drug Treatment

1.	Treatments should be evidence-based in relation to morbidity/mortality prevention.
2.	Use a once-daily regimen which provides 24-hour blood pressure control.
3.	Treatment should be affordable and/or cost-effective relative to other agents.
4.	Treatments should be well-tolerated.
5.	Evidence of benefits of use of the medication in populations to which it is to be applied.



2020 ISH Global Hypertension Practice Guidelines

OPTIMAL

Step 1 Dual low-dose# combination	**A + C** [a, b, c]
Step 2 Dual full-dose combination	**A + C** [a, b]
Step 3 Triple combination	**A + C + D**
Step 4 (Resistant Hypertension) Triple Combination + Spironolactone or other drug*	**A + C +D** **Add Spironolactone (12.5 – 50 mg o.d.)**[d]

a) Consider monotherapy in low risk grade 1 hypertension or in very old (≥80 yrs) or frailer patients.
b) Consider A + D in post-stroke, very elderly, incipient HF or CCB intolerance.
c) Consider A + C or C + D in black patients.
d) Caution with spironolactone or other potassium sparing diuretics when estimated GFR <45 ml/min/1.73m^2 or K^+ >4.5 mmol/L.

- Consider beta blockers when there is a specific indication, e.g.
- heart failure
- , angina
- post-MI
- AF
- young women with or planning pregnancy.

DIABETES

- Bp target <130/80 mm Hg (<140/80 in elderly patients).

- RAS inhibitor (and a CCB and/or thiazide-like diuretic).

- statin in primary prevention if LDL-C >70 mg/dL (diabetes with target organ damage)
- or >100 mg/dL (uncomplicated diabetes).

Treatment strategies in people with diabetes

Recommendations	Class[a]	Level[b]
Antihypertensive drug treatment is recommended for people with diabetes when office BP is ≥140/90 mmHg.[1,226,235,482]	I	A
In people with diabetes receiving BP-lowering drugs it is recommended: • To target SBP to 130 mmHg and <130mmHg if tolerated, but not <120 mmHg.[1,231,235]	I	A

Psychiatric diseases

- BP should be lowered as in the general population,
- preferentially with RAS-inhibitors and diuretics.

- CCBs and alpha1-blockers should be used with care in patients with orthostatic hypotension (eg, SRIs).

Monitoring

- Target:
- Reduce BP at least 20/10 mmHg
- Ideally <= 140/90
- Individualize for elderly based on frailty
- Monitor :
- BP control(achieve target within 3 months)
- Adverse effects
- Long-term adherence
- Referal:
- If BP still uncontrolled , or other issue

• Individualized treatment should be considered according to its tolerability and impact on renal function and electrolytes.	IIa	C
RAS blockers are more effective at reducing albuminuria than other antihypertensive agents, and are recommended as part of the treatment strategy in hypertensive patients in the presence of microalbuminuria or proteinuria.[487,489]	I	A

A combination of two RAS blockers is not recommended.[298]	III	A

Therapeutic strategies in hypertensive patients with CAD

Recommendations	Class[a]	Level[b]
In patients with CAD receiving BP-lowering drugs, it is recommended:		
• To target SBP to ≤ 130 mmHg if tolerated, but not <120 mmHg.[2,496]	I	A
• In older patients (aged ≥65 years), to target to an SBP range of 130–140 mmHg.[2,496]	I	A
• To target DBP to <80 mmHg, but not <70 mmHg.	I	C
In hypertensive patients with a history of myocardial infarction, beta-blockers and RAS blockers are recommended as part of treatment.[503]	I	A
In patients with symptomatic angina, beta-blockers and/or CCBs are recommended.[503]	I	A

In patients with HFpEF, BP treatment threshold and target values should be the same as for HFrEF.[136]	IIa	B
Because no specific drug has proven its superiority, all major agents can be used.	I	C
In all patients with LVH: • It is recommended to treat with an RAS blocker in combination with a CCB or diuretic.[504] • SBP should be lowered to a range of 120–130 mmHg.[504,506]	I IIa	A B

Hypertension and AF

Recommendation	Class[a]	Level[b]
In patients with AF, screening for hypertension is recommended.[536]	I	C
A beta-blocker or non-dihydropyridine CCB should be considered as part of the treatment of hypertension if rate control is needed.[536]	IIa	B
Stroke prevention with oral anticoagulation is recommended in patients with AF and hypertension, and a CHA_2DS_2-VASc score of ≥2 in men and ≥3 in women.[536,556]	I	A
Stroke prevention with oral anticoagulants should be considered in AF patients with hypertension, even when hypertension is the single additional risk factor (CHA_2DS_2-VASc score of 1).[536,556]	IIa	B
Oral anticoagulants should be used with caution in patients with marked BP elevation (SBP ≥180 mmHg and/or DBP ≥100 mmHg); the aim should be to lower SBP to at least <140 mmHg, and SBP lowering to <130 should be considered. If this is not possible, then patients should make an informed decision that they accept that the stroke protection provided by the anticoagulant will be associated with higher bleeding risk.[536]	IIa	B

- ACE inhibitors, ARBs, and beta blockers are associated with a lower risk of AF compared with CCBs.

Hence, RAS blockers should be considered as part of the antihypertensive treatment strategy in hypertensive patients with a high risk of AF (e.g. LVH), to prevent incident AF.

- The magnitude of LVH regression is associated with baseline LV mass, duration of therapy, the SBP reduction, and the drugs used, with ARBs, ACE inhibitors, and CBBs causing more effective LVH regression than beta-blockers or diuretics.

European Heart Journal (2018) 39, 3021–3104

Therapeutic strategies in hypertensive patients with heart failure or LVH

Recommendations	Class[a]	Level[b]
In hypertensive patients with heart failure (with reduced or preserved ejection fraction), BP-lowering treatment should be considered if BP is ≥140/90 mmHg.[c] [136]	IIa	B
In patients with HFrEF, it is recommended that BP-lowering treatment comprises an ACE inhibitor or ARB, and a beta-blocker and diuretic and/or MRA if required.[136]	I	A
Dihydropyridine CCBs may be added if BP control is not achieved.[d]	IIb	C

ESC European Society of Cardiology

European Heart Journal (2018) **39**, 3021–3104
doi:10.1093/eurheartj/ehy339

ESC/ESH GUIDELINES

2018 ESC/ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH)

Authors/Task Force Members: Bryan Williams* (ESC Chairperson) (UK), Giuseppe Mancia* (ESH Chairperson) (Italy), Wilko Spiering (The Netherlands), Enrico Agabiti Rosei (Italy), Michel Azizi (France), Michel Burnier (Switzerland), Denis L. Clement (Belgium), Antonio Coca (Spain), Giovanni de Simone (Italy), Anna Dominiczak (UK), Thomas Kahan (Sweden), Felix Mahfoud (Germany), Josep Redon (Spain), Luis Ruilope (Spain), Alberto Zanchetti† (Italy), Mary Kerins (Ireland), Sverre E. Kjeldsen (Norway), Reinhold Kreutz (Germany), Stephane Laurent (France), Gregory Y. H. Lip (UK), Richard McManus (UK), Krzysztof Narkiewicz (Poland), Frank Ruschitzka (Switzerland), Roland E. Schmieder (Germany), Evgeny Shlyakhto (Russia), Costas Tsioufis (Greece), Victor Aboyans (France), and Ileana Desormais (France)

Hypertension disease staging	Other risk factors, HMOD, or disease	BP (mmHg) grading			
		High normal SBP 130-139 DBP 85-89	Grade 1 SBP 140-159 DBP 90-99	Grade 2 SBP 160-179 DBP 100-109	Grade 3 SBP ≥180 or DBP ≥110
Stage 1 (uncomplicated)	No other risk factors	Low risk	Low risk	Moderate risk	High risk
	1 or 2 risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
	≥3 risk factors	Low to Moderate risk	Moderate to high risk	High Risk	High risk
Stage 2 (asymptomatic disease)	HMOD, CKD grade 3, or diabetes mellitus without organ damage	Moderate to high risk	High risk	High risk	High to very high risk
Stage 3 (established disease)	Established CVD, CKD grade ≥4, or diabetes mellitus with organ damage	Very high risk	Very high risk	Very high risk	Very high risk

Drug	Contraindications	
	Compelling	Possible
Diuretics (thiazides/thiazide-like, e.g. chlorthalidone and indapamide)	• Gout	• Metabolic syndrome • Glucose intolerance • Pregnancy • Hypercalcaemia • Hypokalaemia
Beta-blockers	• Asthma • Any high-grade sinoatrial or atrioventricular block • Bradycardia (heart rate <60 beats per min)	• Metabolic syndrome • Glucose intolerance • Athletes and physically active patients
Calcium antagonists (dihydropyridines)		• Tachyarrhythmia • Heart failure (HFrEF, class III or IV) • Pre-existing severe leg oedema
Calcium antagonists (verapamil, diltiazem)	• Any high-grade sinoatrial or atrioventricular block • Severe LV dysfunction (LV ejection fraction <40%) • Bradycardia (heart rate <60 beats per min)	• Constipation

ACE inhibitors	• Pregnancy • Previous angioneurotic oedema • Hyperkalaemia (potassium >5.5 mmol/L) • Bilateral renal artery stenosis	• Women of child-bearing potential without reliable contraception
ARBs	• Pregnancy • Hyperkalaemia (potassium >5.5 mmol/L) • Bilateral renal artery stenosis	• Women of child-bearing potential without reliable contraception

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HFrEF = heart failure with reduced ejection fraction; LV = left ventricular.

ORIGINAL REPORT

WILEY

Effectiveness of two-drug therapy versus monotherapy as initial regimen in hypertension: A propensity score-matched cohort study in the UK Clinical Practice Research Datalink

Karine Marinier[1] | Pauline Macouillard[2] | Martine de Champvallins[3] | Nicolas Deltour[1] | Neil Poulter[4] | Giuseppe Mancia[5]

- **Results:** Of 54 523 eligible patients, 3256 (6.0%) were initiated to a two-drug combination.
- Of these, 2807 were matched to 5614 mono therapy users. Mean exposure
- duration was 12.7 months, with 76.5% patients changing their initial regimen. Two drug
- therapy was associated with a clinically significant BP control increase in all hypertensive
- patients (HR = 1.17 [95%CI: 1.09-1.26]), more so in patients with grade 2-3
- hypertension (HR = 1.28 [1.17-1.41]). An increase of 27% in BP control (HR = 1.27
- [1.08-1.49]) was observed in patients initiating an ACEi+CCB combination compared
- with initiators of either single class. No significant association was found between
- two-drug therapy and MACE. Several sensitivity analyses confirmed the main findings.
- **Conclusions:** Few patients initiated therapy with two drugs, reflecting UK guidelines'
- recommendation to start with mono therapy. This study supports the greater
- effectiveness of two-drug therapy as the initial regimen for BP control.

Table 21 Major drug combinations used in trials of antihypertensive treatment in a stepped approach or as a randomized combination (combinations vs. placebo or monotherapy)

Trial	Comparator	Type of patients	SBP difference (mmHg)	Outcomes [change in relative risk (%)]
ACE inhibitor and diuretic combination				
PROGRESS[27]	Placebo	Previous stroke or TIA	−9	−28% strokes (P <0.001)
ADVANCE[229]	Placebo	Diabetes	−5.6	−9% micro/macrovascular events (P = 0.04)
HYVET[220]	Placebo	Hypertensive; ≥80 years	−15	−34% CV events (P <0.001)
ARB and diuretic combination				
SCOPE[330]	Diuretic + placebo	Hypertensive; ≥70 years	−3.2	−28% non-fatal strokes (P = 0.04)
CCB and diuretic combination				
FEVER[331]	Diuretic + placebo	Hypertensive	−4	−27% CV events (P <0.001)

ACE inhibitor and CCB combination				
Syst-Eur[332]	Placebo	Older with ISH	−10	−31% CV events (P <0.001)
Syst-China[333]	Placebo	Older with ISH	−9	−37% CV events (P <0.004)
Beta-blocker and diuretic combination				
Coope and Warrender[322]	Placebo	Older hypertensive	−18	−42% strokes (P <0.03)
SHEP[323]	Placebo	Older with ISH	−13	−36% strokes (P <0.001)
STOP-H[324]	Placebo	Older hypertensive	−23	−40% CV events (P = 0.003)
STOP-H 2[334]	ACE inhibitor or conventional antihypertensive	Hypertensive	0	NS difference in CV events
Combination of two RAS blockers/ACE inhibitor + ARB or RAS blocker + renin inhibitor)				
ONTARGET[299]	ACE inhibitor or ARB	High-risk patients		More renal events
ALTITUDE[291]	ACE inhibitor or ARB	High-risk diabetic patients		More renal events

Table 22 Major drug combinations used in trials of antihypertensive treatment in a stepped approach or as a randomized combination (combinations vs. other combinations)

Trial	Comparator	Type of patients	SBP difference (mmHg)	Outcomes [change in relative risk (%)]
ACE inhibitor and diuretic combination				
CAPPP[335]	BB + diuretic	Hypertensive	+3	+5% CV events (NS)
ACCOMPLISH[327]	ACE inhibitor + CCB	Hypertensive with risk factors	+1	+21% CV events (P <0.001)
ARB and diuretic combination				
LIFE[317]	BB + diuretic	Hypertensive with LVH	−1	−26% stroke (P <0.001)
CCB and diuretic combination				
ELSA[336]	BB + diuretic	Hypertensive	0	NS difference in CV events
CONVINCE[233]	BB + diuretic	Hypertensive with risk factors	0	NS difference in CV events
VALUE[337]	ARB + diuretic	High-risk hypertensive	−2.2	−3% CV events (P = NS)
COPE[338]	CCB + BB	Hypertensive	+0.7	NS difference in CV events or stroke

ACE inhibitor and CCB combination				
NORDIL[339]	BB + diuretic	Hypertensive	+3	NS difference in CV events
INVEST[340]	BB + diuretic	Hypertensive with CAD	0	NS difference in CV events
ASCOT[318]	BB + diuretic	Hypertensive with risk factors	−3	−16% CV events (P <0.001)
ACCOMPLISH[327]	ACE inhibitor + diuretic	Hypertensive with risk factors	−1	−21% CV events (P <0.001)
Beta-blocker and diuretic combination				
CAPPP[335]	ACE inhibitor + diuretic	Hypertensive	−3	−5% CV events (P = NS)
LIFE[317]	ARB + diuretic	Hypertensive with LVH	+1	+26% stroke (P <0.001)
ALLHAT[316]	ACE inhibitor + BB	Hypertensive with risk factors	−2	NS difference in CV events
ALLHAT[316]	CCB + BB	Hypertensive with risk factors	−1	NS difference in CV events
CONVINCE[233]	CCB + diuretic	Hypertensive with risk factors	0	NS difference in CV events
NORDIL[339]	ACE inhibitor + CCB	Hypertensive	−3	NS difference in CV events
INVEST[340]	ACE inhibitor + CCB	Hypertensive with CAD	0	NS difference in CV events
ASCOT[318]	ACE inhibitor + CCB	Hypertensive with risk factors	+3	+16% CV events (P <0.001)
Beta-blocker and CCB combination				

CONVINCE[233]	CCB + diuretic	Hypertensive with risk factors	0	NS difference in CV events
NORDIL[339]	ACE inhibitor + CCB	Hypertensive	−3	NS difference in CV events
INVEST[340]	ACE inhibitor + CCB	Hypertensive with CAD	0	NS difference in CV events
ASCOT[318]	ACE inhibitor + CCB	Hypertensive with risk factors	+3	+16% CV events (P <0.001)
Beta-blocker and CCB combination				
COPE[329]	ARB + CCB	Hypertensive	+0.8	NS difference in CV events or stroke
ARB and CCB combination				
COPE[329]	CCB + diuretic	Hypertensive	−0.7	NS difference in CV events or stroke
COPE[329]	CCB + BB	Hypertensive	−0.8	NS difference in CV events or stroke
COLM[328]	ARB + diuretic	Older hypertensive	0	NS difference in CV events

ACCOMPLISH = Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension; ACE = angiotensin-converting enzyme; ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ARB = angiotensin receptor blocker; ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; BB = beta-blocker; CAD = coronary artery disease; CAPPP = Captopril Prevention Project; CCB = calcium channel blocker; COLM = Combination of OLMesartan and a calcium channel blocker or diuretic in Japanese elderly hypertensive patients; CONVINCE = Controlled Onset Verapamil Investigation of Cardiovascular End Points; COPE = Combination Therapy of Hypertension to Prevent Cardiovascular Events; CV = cardiovascular; ELSA = European Lacidipine Study on Atherosclerosis; INVEST = International Verapamil-Trandolapril Study; LIFE = Losartan Intervention For Endpoint reduction in hypertension; LVH = left ventricular hypertrophy; NORDIL = Nordic Diltiazem; NS = non-significant; SBP = systolic blood pressure; VALUE = Valsartan Antihypertensive Long-term Use Evaluation.

ACE inhibitors side effects

- Cough
- Hypotension
- Reduce GFR(Avoid in volume depletion)
- Hyperkalemia
- Angioedema
- Anemia

Calcium – Channel Blockers
Mechanism of action:

- Rank order of **potency** :
  Dihydropyridines>diltiazem> verapamil

- For negative **chronotropic & inotropic**:
  Verapamil>>diltiazem>>dihydropyridines

Therapeutic Principles:

- Short acting dihydropyridines should not be used to treat hypertension.
- The safety and efficacy of long acting dihydropyridines was confirmed by ALLHAT & VALUE study.
- Dihydropyridine CCBs should not be used as first line therapy in proteinuric hypertensives.

Side Effects

- Dihydropyridine CCBs :
- Headache
- Flushing
- Ankle edema
- CHF
- Gingival hyperplasia
- Esophegeal reflux

Class members

- Non selective β-adrenergic antagonism (Propnalolol,Nadolol,Timolol)
- Non selective β-adrenergic antagonism with partial agonist actvity.(Carteolol,Pindolol)
- β1 – selective adrenergic antagonism (Atenolol, metoprolol)
- β1 – selective adrenergic antagonism with partial agonist activity(Acebutolol)
- Non selective β-adrenergic antagonism with α1-adrenergic antagonism (labetalol,Carvedilol)

- They may result in impaired glucose intolerance & ↑BS in some diabetic patients.
- Labetalol commonly used in pregnancy.
- Abrupt withdrawal may be associated with overshoot HTN & worsening angina in patients with CAD.

- In ALLHAT study , the thizide –type diuretic chlorthalidone was as effective as newer more expensive agents in lowering BP & in preventing cardiovascular complications.

- Combination with other classes exert a synergistic effect.

- The most common cause of drug resistant hypertension is failure to include diuretic.

- Thiazides , because of their long half-lives,are much more effective than loop diuretcs.
- Low dose hydrochlorthizide (12.5 mg/day)often in fixed dose combination is recommended for uncomplicated hypertension.
- Loop diuretics are the choice in CKD or HF.
- Because of short half life of furosemide , torsemide is a better choice.

Original Article

Hypertension, antihypertensive treatment and cancer incidence and mortality: a pooled collaborative analysis of 12 Australian and New Zealand cohorts

Jessica L. Harding[a,b], Manoshayini Sooriyakumaran[a,b], Kaarin J. Anstey[c], Robert Adams[d], Beverley Balkau[e], Sharon Brennan-Olsen[m,n], Tom Briffa[f], Timothy M.E. Davis[g], Wendy A. Davis[g], Annette Dobson[h], Graham G. Giles[i], Janet Grant[j], Rachel Huxley[h], Matthew Knuiman[f], Mary Luszcz[k], Paul Mitchell[l], Julie A. Pasco[m,n], Christopher M. Reid[o], David Simmons[p,q], Leon A. Simons[r], Anne W. Taylor[j], Andrew Tonkin[s], Mark Woodward[t,u], Jonathan E. Shaw[a,b,*], and Dianna J. Magliano[a,b,*]

Journal of Hypertension 2016, 34:149–155

- Background: Observational studies examining associations
- between hypertension and cancer are inconsistent. We
- explored the association of hypertension, graded
- hypertension and antihypertensive treatment with cancer
- incidence and mortality.

- Method
- 86593 participants from the Australian and New Zealand
- Diabetes and Cancer Collaboration were linked to the National Death Index and Australian Cancer Database.

- Results: Over a median follow-up of 15.1 years, 12 070 incident
- and 4350 fatal cancers were identified.
- -
- . Untreated and treated hypertension, compared with normo-tension were associated with an increased risk for cancer incidence
- [hazard ratio 1.06, 95% CI (1.00–1.11) and1.09 (1.02–1.16) respectively], and cancer mortality (1.07, 0.98–1.18) and (1.15
- , 1.03–1.28), respectively.

- .When compared with untreated hypertension, treated hypertension
- did not have a significantly greater risk for cancer incidence
- (1.03, 0.97–1.10) or mortality (1.07, 0.97–1.19).
-

- A significant dose–response relationship was observed between gradedhypertension and cancer incidence and mortality.
- When stratified by treatment status, these relationships remained significant in untreated, but not in treated, hypertension.
- .
- Conclusion:
- Hypertension, both treated and untreated, is associated with a
- modest increased risk for cancer incidence and mortality.
- Similar risks in treated and untreated hypertension suggest
- that the increased cancer risk is not explained by the use
- of antihypertensive treatment.

REVIEW

Triple-combination therapy in the treatment of hypertension: a review of the evidence

R Düsing[1], B Waeber[2], M Destro[3], C Santos Maia[4] and P Brunel[4]

- Journal of human hypertension 2017

Hypertension is a serious public health concern with inadequate control of blood pressure (BP) worldwide. Contributing factors include low efficacy of drugs, underuse of combination therapies, irrational combinations, physicians' therapeutic inertia and poo adherence to treatment. Current guidelines recommend the use of initial (dual) combination therapy in high-risk patients for immediate BP response, better short- and long-term BP control, and continued/improved patient adherence. This article aims to review the existing evidence of triple-combination therapies with respect to efficacy, safety and adherence to treatment. It is estimated that three drugs are required to achieve BP control in approximately one-fourth to one-third of patients. Randomised controlled tri odipine/olmesartan, hydrochlorot ater proportions of patients achi nbination therapy is efficacious fo . Both RCTs and post-marketing observational studies have shown consistent and comparable efficacy in both the general population and high-risk hypertensive subgroups. Triple therapies are generally well tolerated with adverse event profiles similar to dual regimens. In addition, fixed-dose combinations used as single pill improve patient adherence leading to better long-term BP control. Depending on regional circumstances, they may also be cost effective. Thus, single-pill triple combinations of different classes of drugs with complementary mechanisms of action help to treat patients to goal with improved efficacy and better adherence to treatment.

Triple combination therapy is efficacious for moderate to severe hypertension , with substantial BP reduction over dual regimens.

Journal of Human Hypertension advance online publication, 23 February 2017; doi:10.1038/jhh.2017.5

Study	Study design	N	Triple combination	Dual comparator in the studies	BP reductions with triple vs dual therapies
Triple antihypertensive therapy with Aml, Val and HCTZ: a randomised clinical trial[20]	Multicentre, randomised, double-blind, parallel-group, 8-week study in patients with moderate to severe hypertension	2271	Aml/Val/HCTZ (10/320/ 25 mg)	Aml/Val (10/320 mg) Val/HCTZ (320/25 mg) Aml/HCTZ (10/25 mg)	Change (LS mean) from baseline to week 8 for triple vs respective dual combinations in SBP: −39.7 vs −32.0, −33.5 and −31.5 mm Hg DBP: −24.7 vs −19.7, −21.5 and −19.5 mm Hg
Triple therapy with Olm, Aml and HCTZ in adult patients with hypertension[21]	Multicentre, randomised, double-blind, parallel-group, 12-week study in patients with moderate to severe hypertension	2492	Aml/Olm/ HCTZ (10/40/ 25 mg)	Olm/Aml (40/10 mg) Olm/HCTZ (40/25 mg) Aml/HCTZ (10/25 mg)	Change from baseline (LS mean) to week 12 for triple vs respective dual combinations in SBP: −37.1 mm Hg vs −30.0, −29.7 and −27.5 mm Hg DBP: −21.8 vs −18.0, −16.9, and −15.1 mm Hg
Triple-drug combination of Tel, Aml and HCTZ in the treatment of essential hypertension[22]	Randomised, single-blind, 12-week study in patients with moderate to severe hypertension	220	Aml/Tel/HCTZ (5/40/12.5 mg)	Tel/HCTZ (40/12.5 mg)	Reduction in mean sitting SBP/DBP from baseline to end of week 12 from 166.84/103.62 to 123.05/81.17 mm Hg for triple vs 168.89/105.43 to 130.93/84.24 mm Hg with dual therapy
Efficacy and safety of aliskiren-based dual and triple-combination therapies in US minority patients with stage 2 hypertension[60]	Randomised, double-blind, active-controlled, parallel-group, forced-titration 8-week study in patients with stage 2 hypertension	412	Aml/Ali/HCTZ (5/150/ 12.5 mg)	Aml/Ali (5/150 mg)	Change (LS mean) from baseline to week 8 for triple vs dual combination in SBP: −36.5 vs −29.5 mm Hg DBP: −15.1 vs −12.0 mm Hg

Abbreviations: Aml, amlodipine; Ali, aliskiren; BP, blood pressure; DBP, diastolic blood pressure; HCTZ, hydrochlorothiazide; LS, least square; Olm, olmesartan; RCTs, randomised controlled trials; SBP, systolic blood pressure; Tel, telmisartan; Val, valsartan.

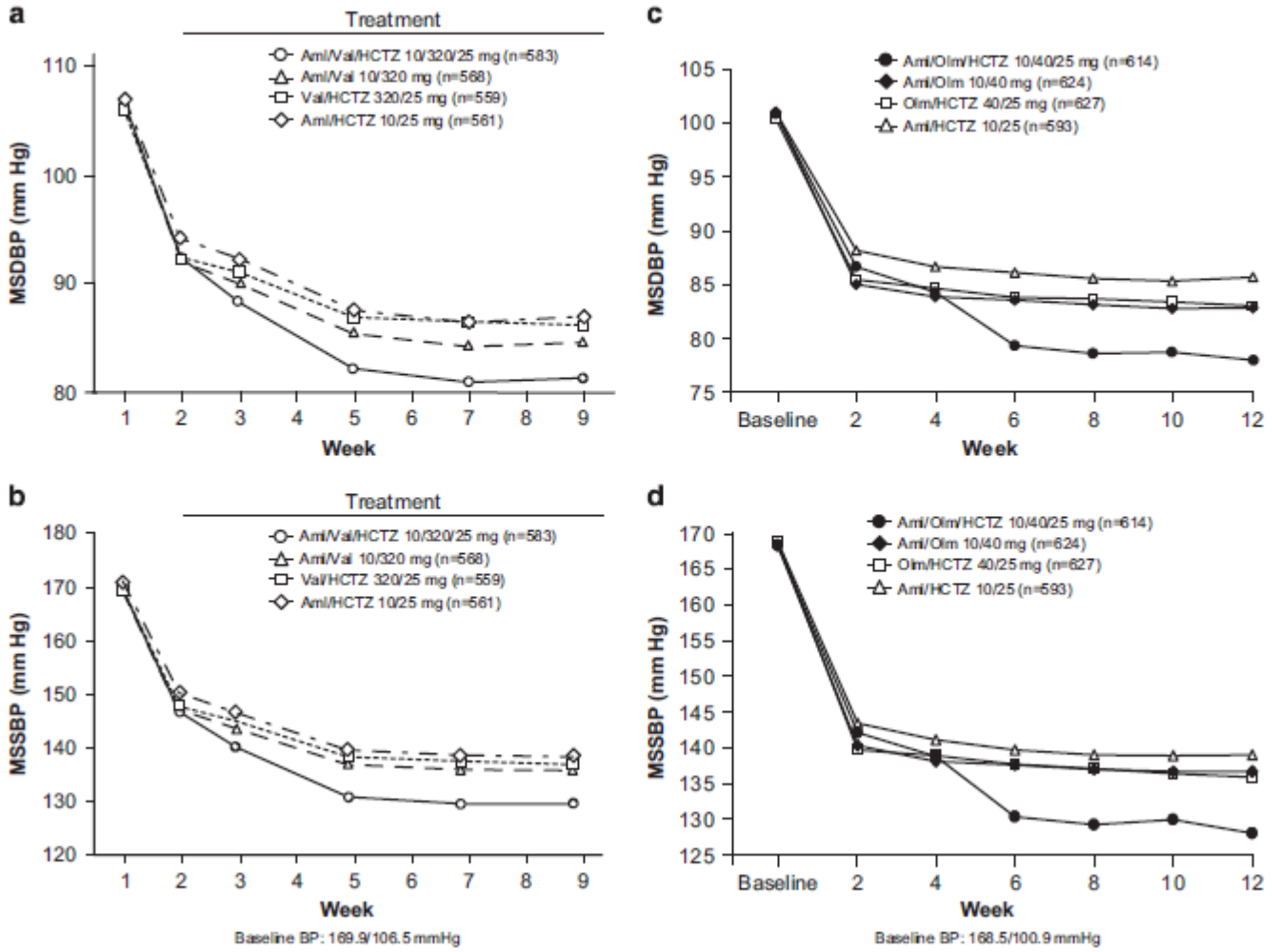
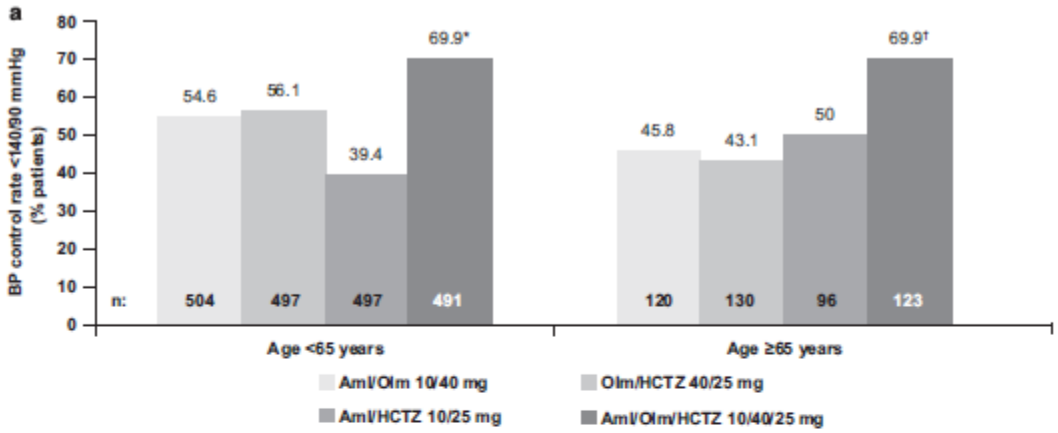
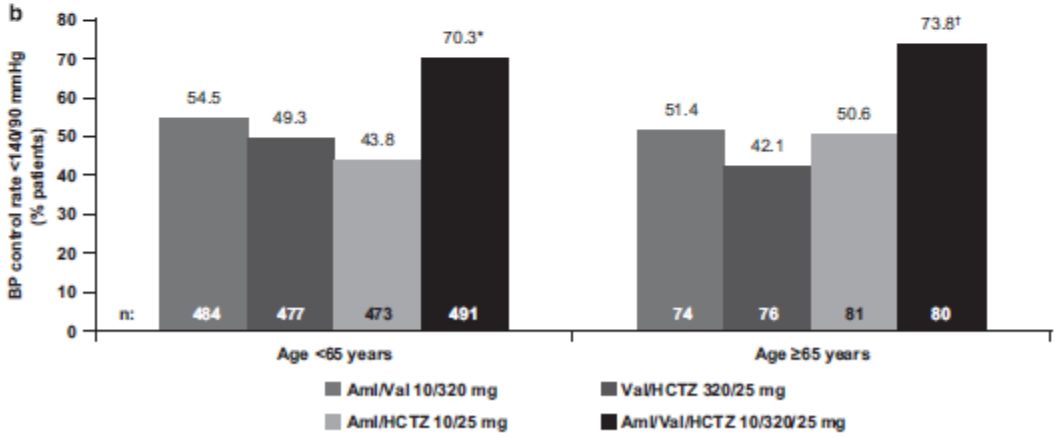


Figure 1. Triple-combination therapies with Aml/Val/HCTZ[20] and Aml/Olm/HCTZ[21] provide early reductions in DBP (**a**,**c**) and SBP (**b**,**d**) from baseline compared with dual therapies. MSDBP, mean sitting diastolic blood pressure; MSSBP, mean sitting systolic blood pressure.



*p<0.0001, †p≤0.005 vs each dual-combination treatment within age subgroup



*p<0.0001 vs. each dual therapy; †p<0.01 vs. each dual therapy

Figure 4. Triple-combination therapy with Aml/Olm/HCTZ[31] (**a**) and Aml/Val/HCTZ[28] (**b**) enabled better BP control compared with dual therapies, independent of age.

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https://doi.org/10.1007/s11906-018-0866-y

RESISTANT HYPERTENSION (L DRAGER, SECTION EDITOR)

Resistant Hypertension: Time to Consider the Best Fifth Anti-Hypertensive Treatment

Andrea Pio-Abreu[1] · Luciano F. Drager[1,2]

Abstract

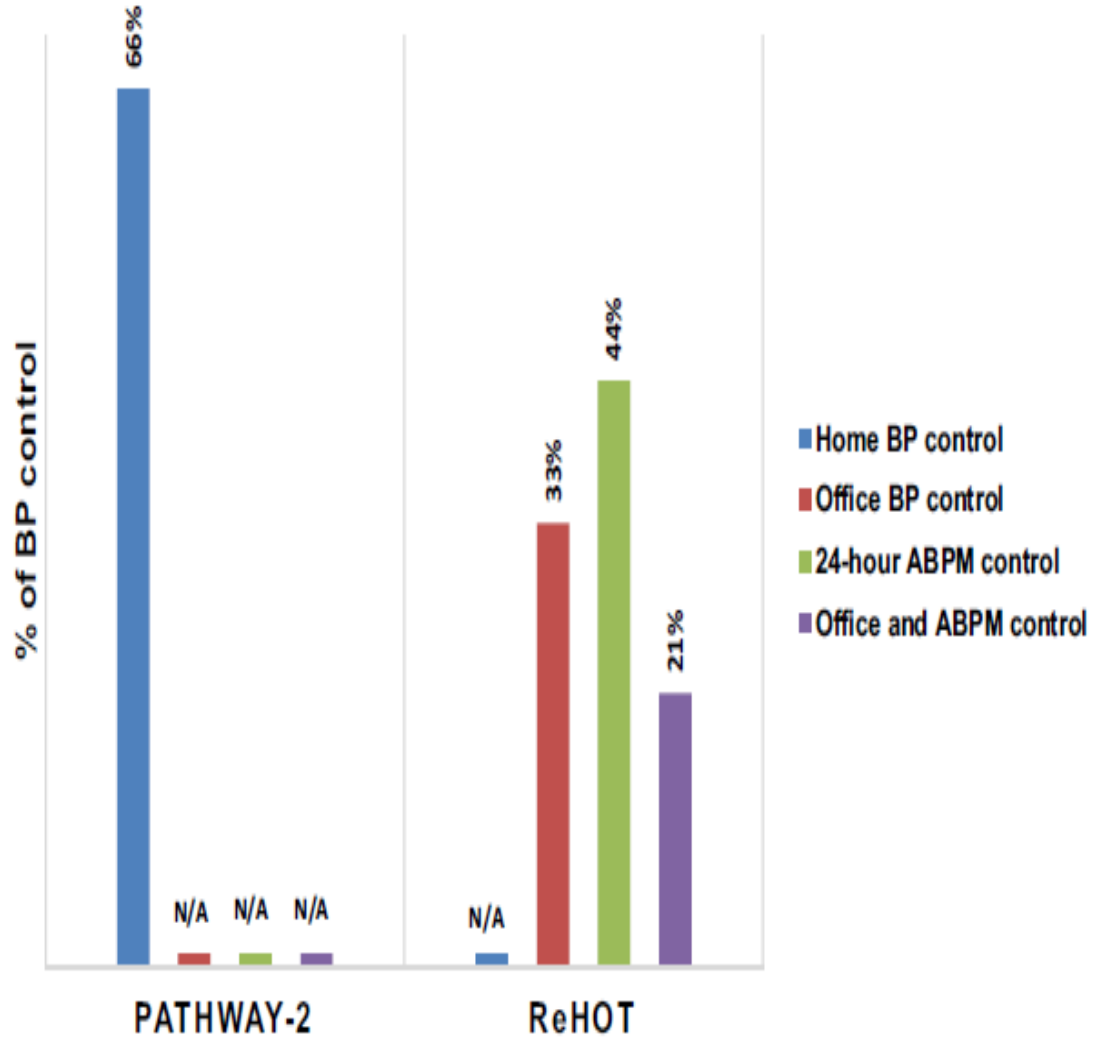
Purpose of Review Resistant hypertension (RH) is a growing clinical condition worldwide associated with target-organ damage and poor prognosis compared to non-resistant counterparts. The purpose of this review is to perform a critical evaluation of preferable drug choices for managing RH highlighting the evidence that significant proportion of patients remained uncontrolled despite using four anti-hypertensive drugs.

Recent Findings Until recently, the fourth drug therapy was main derived from personal opinion or small interventional studies. The recent data derived from two multicentric randomized trials, namely PATHWAY-2 and ReHOT, pointed spironolactone as the preferable fourth drug therapy in patients with confirmed RH as compared to bisoprolol and doxazosin (PATHWAY-2) as well as clonidine (ReHOT). However, significant proportion of patients (especially observed in ReHOT trial that used 24-h ambulatory blood pressure monitoring) did not achieve optimal blood pressure with the fourth drug. This finding underscores the need of new approaches and treatment options in this important research area.

Summary The current evidence pointed that significant proportion of RH patients are requiring more than four drugs for controlling BP. This statement is particularly true considering the new criteria proposed by the 2017 Guidelines for diagnosing RH (> 130 × 80 mmHg). New combinations, drugs, or treatments should be tested aiming to reduce the RH burden. Based on the aforementioned multicentric trials, we proposed the first five preferable anti-hypertensive classes in the overall context of RH.

Keywords Resistant hypertension · Treatment · Spironolactone · Clonidine · Blood pressure

Fig. 1 Rate of blood pressure control with spironolactone in the PATHWAY-2 and ReHOT trials. N/A not available



The "top three" classes (not necessarily in this order)	Thiazide diuretics
	ACEi or ARB
	Calcium channel blockers
Fourth preferable drug*#	Spironolactone
Fifth preferable drug#	Clonidine (at moderate doses)

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Nanocarriers as treatment modalities for hypertension

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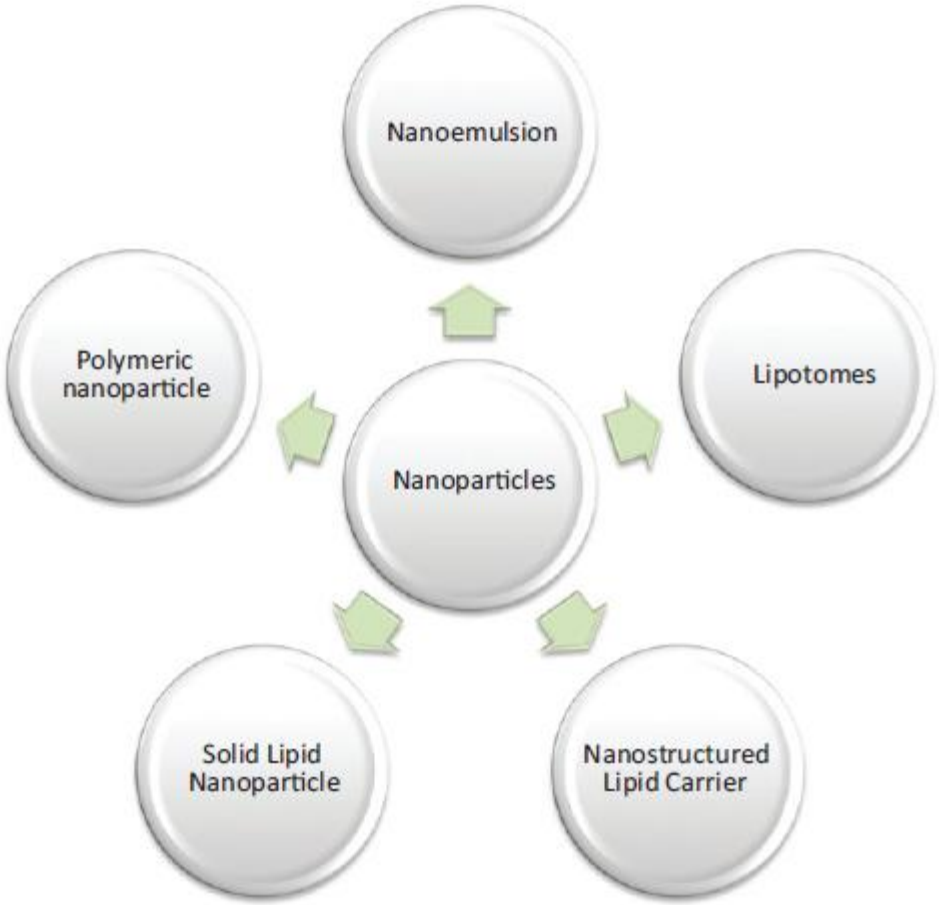

Figure 2. Diagram for currently used nanoparticles utilized in the treatment of hypertension.

Table 3. Novel delivery system of antihypertensives and their positive outcome.

Type of delivery system	Therapeutic system	Excipients used	*In-vivo* study model	Comments
Polymeric nanoparticle	Ramipril	lecithin/chitosan	Male Wistar rats	1.6-fold decrease in systolic blood pressure
	Nifedipine	PCL PLAGA Eudragit RL/RS	Male adult SHR	Initial fall in systolic blood pressure was rapid for PEG solution followed by with PCL NP and PLAGA NP. Blood pressure was within normal range after 10 h of dosing with all three NPs while PEG solution failed to achieve such sustained effect.
	Felodipine	PLGA, Pluronic F-68	Male Wistar rats	Systolic blood pressure normalized and elevated ST segment of ECG became normal upto a period of 3 days as compared to drug suspension.
	Lercanidipine	HPMC, TPGS	Male Sprague–Dawley rats	2.47 increase in oral bioavailability than raw drug without TPGS
	Aliskiren	Magnetite, poly (D, L-lactide), Pluronic F-68	Male spontaneously hypertensive rats	Significant decrease in mean systolic blood pressure by aliskiren nanoparticle as compared to aliskiren suspension and placebo
Solid Lipid nanoparticle	Nisoldipine	Trimyristin (TM; Dynasan-114; glyceryl trimyristate), egg lecithin, Poloxamer-188	Male Wistar rats	2.17 times increase in oral bioavailability, significant reduction in systolic blood pressure for a period of 36 h
	Candesartan Cilexetil	GMS, soy lecithin, Tween 80	Male Sprague–Dawley rats	12 times increase in oral bioavailability
	Isradipine	Trimyristin or GMS, poloxamer 188	Wistar rats	Significant decrease in the systolic blood pressure with SLN formulation using two different lipids
Nanostructured Lipid Carrier	Lacidipine	GMS, Linoleic acid and poloxamer 407	Wistar male albino rats	3.9 times enhancement in the relative bioavailability
	Lercanidipine	Labrafil 2130M, GMS, linseed oil and Tween 80	Male Sprague–Dawley rats	24 h control on the blood pressure by NLC as compared to plain drug suspension
Nanoemulsion	Ramipril	Sefsol 218, Tween 80, carbitol	Wistar male albino rats	229.62% increase in relative bioavailability of ramipril nanoemulsion as compared to ramiprol marketed capsule and 539.49% increase in bioavailability of formulation as compared to drug suspension.
	Amlodipine	DE (Labrafilm 1944 CS and Dextrin)	Male Sprague–Dawley rats	In vitro release studied showed higher release of amlodipine from DE than powdered drug. 2.6 to 2.9 times increase in C_{max} and AUC (0–24h) from DE than powder. Marked reduction in photodegradation of drug in DE than powdered drug (5.6% versus 66.9%)
	Olmesartan Medoxomil (Reg et al., 2015)	SNEDDS (SNEOF and CSNEOF)	Unisex Wistar rats	After 0.5 h of dosing, significant reduction in arterial blood pressure (180 to 189 mm Hg) was seen with SNEOF (141 ± 1.36), CSNEOF (136 ± 1.45), and marketed formulation (138 ± 1.08). After 48 h of study, rats were found

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	Amlodipine	DE (Labrafilm 1944 CS and Dextrin)	Male Sprague–Dawley rats	In vitro release studied showed higher release of amlodipine from DE than powdered drug. 2.6 to 2.9 times increase in C_{max} and AUC (0–24h) from DE than powder. Marked reduction in photodegradation of drug in DE than powdered drug (5.6% versus 66.9%)
	Olmesartan Medoxomil (Beg et al., 2015)	SNEDDS (SNEOF and CSNEOF)	Unisex Wistar rats	After 0.5 h of dosing, significant reduction in arterial blood pressure (180 to 189 mm Hg) was seen with SNEOF (141 ± 1.36), CSNEOF (136 ± 1.45), and marketed formulation (138 ± 1.98). After 48 h of study, rats were found normotensive (BP < 130 mm Hg) with SNEOF and CSNEOF
	Valsartan	S-SNEDDS (Capmul MCM, Labrasol, Tween 20)	Male Wistar rats	3–3.5 time increase in the rate of dissolution, significant reduction in the mean systolic blood pressure after 0.5 h and 2 h of dosing of S-SNEDDS as compared to valsartan suspension showing faster onset of action of S-SNEDDS thus showing it to have the potential of the bioavailability enhancement of valsartan
	Lacidipine	S-SNEDDS (Labrafil and capmul as oil, Cremophor and Tween 80 as surfactant and transcutol as co-surfactant)	Male Wistar rats	Rate of dissolution increased significantly
	Carvedilol	S-SNEDDS (Capmul MCM, Nikkol HCO 50) L-SNEDDS (Cremophor EL, Transcutol HP)	——	2.34 and 1.85 times enhancement in C_{max} and AUC, respectively of S-SNEDDS, thus showing increase in the bioavailability.
Lipotomes	Lacidipine	Cetyl alcohol and Tween 80	Adult male human volunteer	540.11% increase in relative bioavailability of enteric-coated capsule of lipotome as compared to Motens tablet

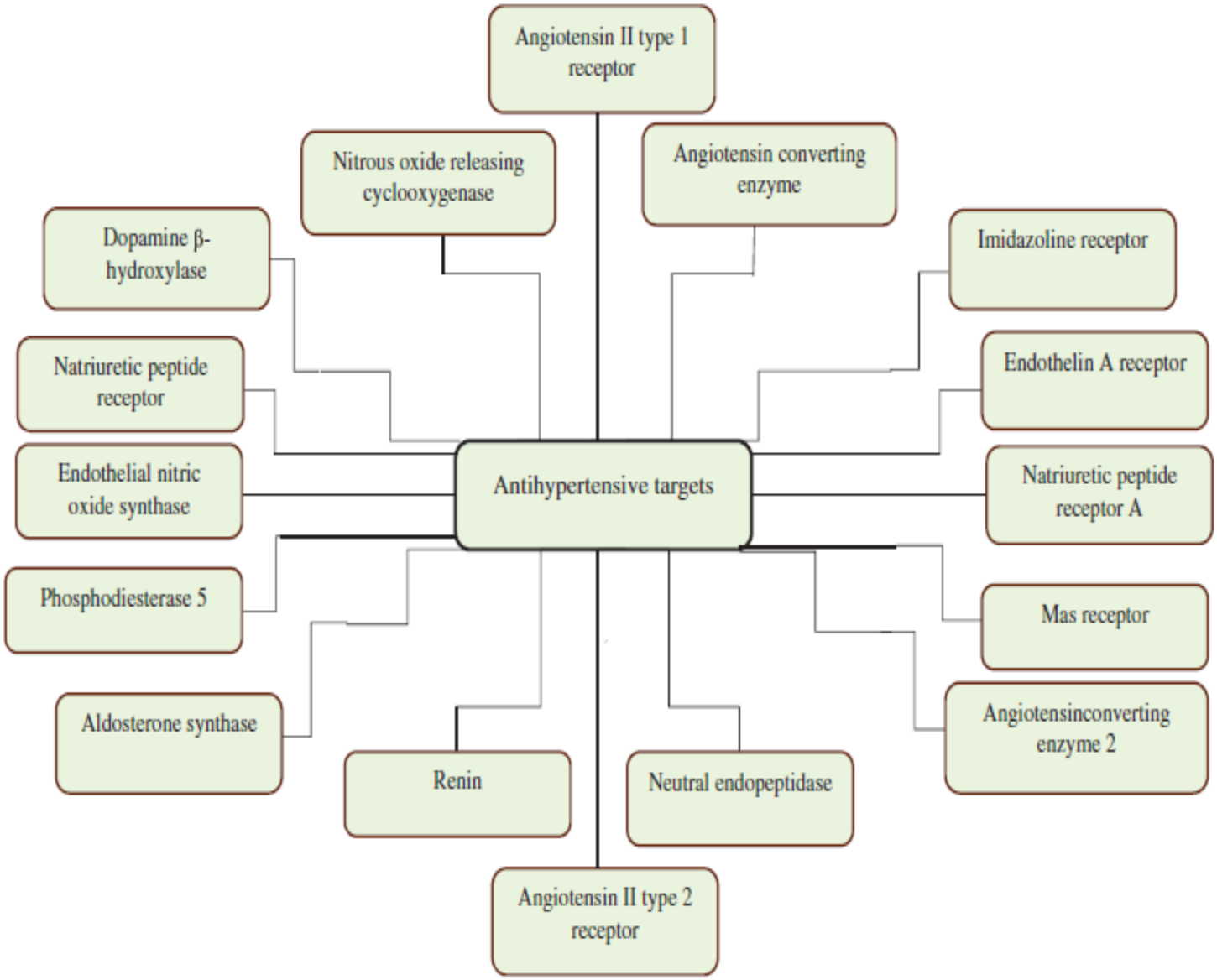

Figure 1. Novel molecular targets for antihypertensives.

			Vitae Pharmaceuticals, USA	
Endothelin A receptor antagonist	Macitentan (PAH)	Marketed	Actelion Pharmaceuticals	Palatin Technologies, Inc [Online];
	Ambrisentan (PAH)	Marketed	Gilead	Paulis & Unger (2010)
Imidazoline-receptor blocker	Monoxidine	Marketed	Eli Lilly, USA	Paulis et al. (2015)
Natriuretic peptide receptor agonist	PL3994	Phase II	Palatin Technologies, USA	Pridgen et al. (2014)
Endothelila nitric oxide synthase coupler	Cicletanine	Marketed	Gilead Sciences, Inc	Antal et al. (2015); Ranpise et al. (2014)
NO-releasing COX inhibitor	Naproxcinod	Phase III	NicOx, France	Selvamuthukumar & Velmurugan (2012).
Mas GPCR receptor	CGEN-856	Preclinical	BioLineRx	Shafiq et al. (2007)

PAH: pulmonary arterial hypertension, ACE: angiotensin-converting enzyme, AT1R: angiotensin II type 1 receptor, AT2R: angiotensin II type 2 receptor, PPAR-γ: peroxisome proliferator-activated receptor gamma.

Novel antihypertensive Drugs

Table 1. Some novel antihypertensives with their development phase and mechanism of action.

Mechanism	Drug	Development phase	Company	References
Aldosterone-receptor blocker	Eplerenone	Marketed	Pfizer, USA	ACE 2 modulator
Phosphodiesterase 5 inhibitor	Tadalafil	Marketed	Eli Lilly, USA	ACE 2 modulator ;
	KD027	Phase II	Kadmon Pharmaceuticals	Adis Insight
Dopamine β-hydroxylase inhibitor	Etamicastat	Phase I	Bial, Portugal	McLendon et al. (2015)
ACE 2 modulator	APN01 (rhACE2)	Phase II	Apeiron-biologics	Morrell et al. (2013)
Aldosterone synthase inhibitor	ASI LCI699	Phase II	Novartis, Switzerland	Muller et al. (2000)
ACE inhibitor	Imidapril	Marketed	Mitsubishi Tanabe Pharma	Nolte et al. (2011)
AT1R blocker with PPAR-γ activity	Azilsartan (TAK-491)	Marketed	Takeda Pharmaceuticals, Japan	Novartis' new heart failure medicine LCZ696, now called Entresto(TM), approved by FDA to reduce risk of cardiovascular death and heart failure hospitalization [Online]
AT2R agonist	Compound 21	Phase I	Vicore, Sweden	Nunes et al. (2010)
Combined AT1R blocker and NEP inhibitor	LCZ696	Phase III	Novartis, Switzerland	O'Driscoll & Griffin (2008); Ohara-ch [Online]
	Daglutril	Phase II	Solvay, Belgium	
Renin inhibitor	Aliskiren	Marketed	Novartis, Switzerland, and Speedel Switzerland	ACE 2 modulator; Oparil & Schmieder (2015)
	VTP27999	Phase II		

State-of-the-Art Review

State-of-the-Art review: Hypertension practice guidelines in the era of COVID-19

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- 417 COVID-19 patients with HTN from China, the data suggest ACEI/ARB therapy attenuated the inflammatory response, potentially through the inhibition of IL-6 levels.

- ACEI/ARB therapy has a beneficial effect on the immune system by avoiding peripheral T cell depletion.

- Dihydropyridines CCBs (nifedipine and amlodipine) may be a benefit for the treatment of hypertensive patients withCOVID-19.

- In a retrospective analysis, a small cohort of elderly hypertensive patients treated with a CCB during a COVID-19 infection, had a significantly higher survival rate and were much less likely to require mechanical intubation (50% vs. 14.6%, respectively.