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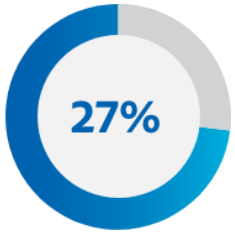
# Evaluation of the efficacy and tolerability of a fixed dose COMBInation of amlodipiNe and indapamidE in patients older than 55 years

COMBINE trial

# Hypertension situation in Bangladesh

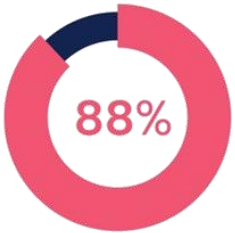





Hypertensive population


Not Aware


Taking medication




Uncontrolled on medication


Hypertensive Patients
> 55 years of age

COMBINE trial

Ref: 1. Bangladesh Demography and Health Survey 2018 2. Journal of Human Hypertension (2018) 32:668–680

# The problems are

POOR CONTROL RATE

LOW TREATMENT ADHERENCE

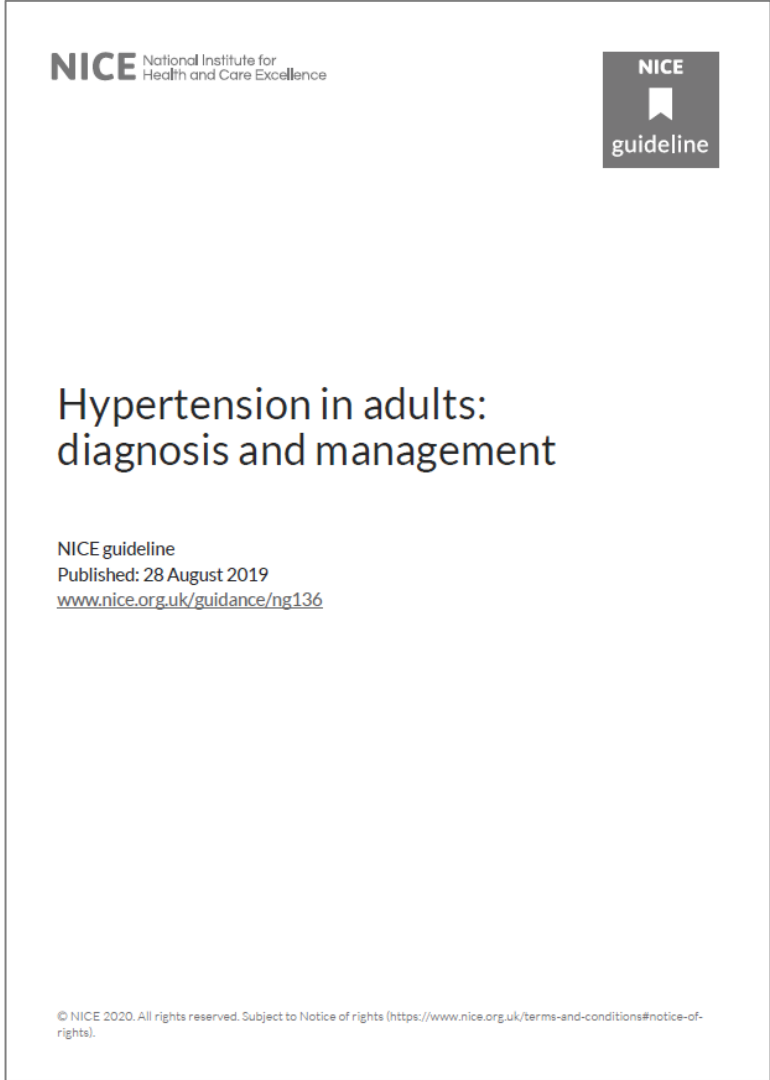
COMBINE trial

# Guidelines recommend prescribing single pill combinations




**BHS-NICE 2019** guideline categorizes hypertensive patients in two groups:

- **below 55 years**
- **55 years or above**




Treatment options for hypertensive **patients aged 55 or above**

- Calcium Channel Blocker (**Amlodipine**/others)
- Thaiazide/Thiazide-like diuretic (**Indapamide**/Chlorthalidone)

COMBINE trial

# Investigators

| Sl. No. | Investigator Name | Institution |
|---|---|---|
| 1 | Prof. Quazi Tarikul Islam | Popular Medical College |
| 2 | Prof. KMHS Sirajul Haque | Anwar Khan Modern Medical College |
| 3 | Prof. Kaniz Moula | United Hospital |
| 4 | Prof. H.A.M. Nazmul Ahsan | Popular Medical College |
| 5 | Prof. Khan Abul Kalam Azad | Popular Medical College |
| 6 | Prof. Md. Mujibur Rahman | Popular Medical College |
| 7 | Prof. Ismail Patwary | Sylhet Womens' Medical College |
| 8 | Prof. Md. Zakir Hossain | TMSS Medical College, Bogura |
| 9 | Prof. Md. Titu Miah | Dhaka Medical College |
| 10 | Prof. Abul Kalam Azad | BSMMU |







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# Research Assistants

| Sl. No. | Name | Designation | Institution | Investigator |
|---|---|---|---|---|
| 1 | Dr. Refaya Tasnim | FCPS Trainee | BSMMU | Prof. Quazi Tarikul Islam |
| 2 | Dr. Muhaiminul Hoque | Emergency Medical Officer | Islami Bank Medical College & Hospital, Rajshahi | Prof. KMHS Sirajul Haque |
| 3 | Dr. Sumaiya Kabir | Indoor Medical Officer | Aurora Specialized Hospital, Dhaka | Prof. Kaniz Moula |
| 4 | Dr. Tasnim Khan | Lecturer | MH Samorita Hospital & Medical College, Dhaka | |
| 5 | Dr. Ishrat Binte Reza | Assistant Professor (Medicine) | Popular Medical College, Dhaka | Prof. HAM Nazmul Ahasan |
| 6 | Dr. Mahbub Mayukh Rishad | Assistant Professor (Medicine) | Popular Medical College, Dhaka | Prof. Khan Abul Kalam Azad |
| 7 | Dr. Nawsabah Noor | Assistant Professor (Medicine) | Popular Medical College, Dhaka | |
| 8 | Dr. Tasmina Chowdhury | Assistant Professor (Medicine) | Popular Medical College, Dhaka | |
| 9 | Dr. Moona Farzana Razzaque | Indoor Medical Officer | Sylhet Womens' Medical College | Prof. Md. Ismail Patwary |
| 10 | Dr. Mehrangis Rahman | FCPS Part-II Trainee | Dhaka Medical College | Prof. Md. Mujibur Rahman |
| 11 | Dr. Sarwar E Alam | Resident Physician | Shaheed Ziaur Rahman Medical College, Bogura | Prof. Md. Zakir Hossain |
| 12 | Dr. Farhana Ahmed | FCPS Part-II Trainee | Dhaka Medical College | Prof. Md. Titu Miah |
| 13 | Dr. Atikur Rahman | Medical Officer | Mugda Medical College & Hospital, Dhaka | Prof. Md. Abul Kalam Azad |

COMBINE trial

# Objectives

- To assess the antihypertensive efficacy and tolerability of a fixed dose combination of **amlodipine/indapamide**
- To evaluate the effect on patients' well-being using the visual analogue scale (VAS)
- To assess the opinion of doctors and patients on the efficacy and tolerability of fixed dose combination therapy with amlodipine/indapamide

COMBINE trial

## Type of trial

Multicenter, open-label, observational trial

## Duration

**3** months

# Inclusion criteria

- Age 55 years or older
- Diagnosis of primary arterial hypertension
- Suboptimal efficacy of previous antihypertensive therapy with clinical SBP 140-179 mmHg; or untreated grade 1-2 HT with clinical SBP 140-179 mmHg, in patients requiring therapy with amlodipine and indapamide
- Pulse pressure 60 mmHg or higher
- Consent of the patient to participate in the program
- Absence of contraindications to the prescription of **Amlodipine-Indapamide combination**

COMBINE trial

# Exclusion criteria

- Clinical BP ≥180/110 mmHg on the top of treatment or ≥200/110 mmHg if untreated
- Resistant hypertension
- Known or suspected symptomatic orthostatic hypotension
- History of MI/Cerebrovascular incident/Unstable angina within the 6 months
- Congestive heart failure of NYHA class III-IV
- Type 1 diabetes mellitus or decompensated type 2 diabetes mellitus
- Contraindications or known intolerance to diuretics or CCB (indapamide and amlodipine)

COMBINE trial

# Treatment & Material/Methods

## Treatment

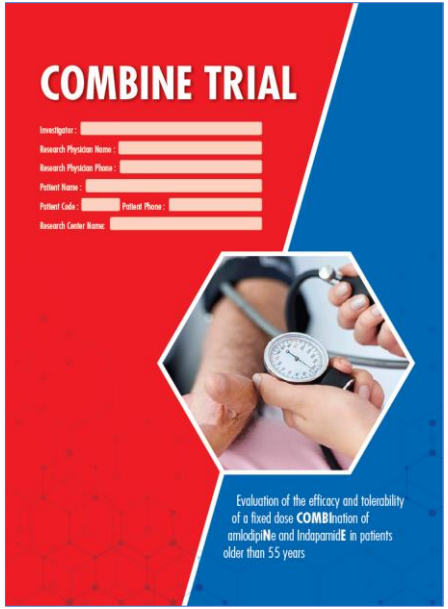
- The patient is included in the program if the doctor decides to adjust or initiate antihypertensive therapy by prescription of **Amlodipine-Indapamide combination**

## Material & methods

- The program is planned to enroll patients with grade 1-2 HT who have not achieved BP control on the top of previous monotherapy or who did not previously receive antihypertensive therapy
- The office BP values will be measured by digital BP machine at regular visits
- The BP self-monitoring by patients at home with the keeping of self-monitoring diaries
- Self-evaluation of the patient's well-being using the visual-analogue scale (VAS)
- Assessment of adverse events, with completion of the pharmacovigilance form (if necessary)

COMBINE trial

# Material and methods




Patient information folder


| তারিখ | বসে থাকা অবস্থায় | | দাড়ানোর ১ মিনিট পর | | দাড়ানোর ৩ মিনিট পর | |
|---|---|---|---|---|---|---|
| | SBP | DBP | SBP | DBP | SBP | DBP |
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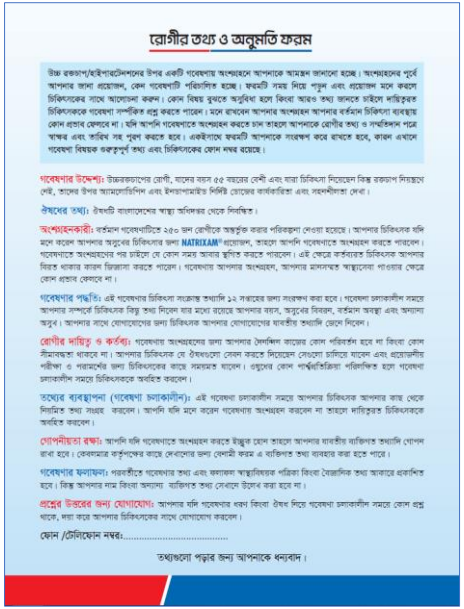
Blood pressure diary



রোগীর তথ্য ও অনুমতি ফরম

উচ্চ রক্তচাপ/হাইপারটেনশনের উপর একটি গবেষণায় অংশগ্রহণে আপনাকে আমন্ত্রণ জানানো হচ্ছে। অংশগ্রহণের পূর্বে আপনার জানা প্রয়োজন, কেন গবেষণাটি পরিচালিত হচ্ছে। ফরমটি সময় নিয়ে পড়ুন এবং প্রয়োজন মনে করলে চিকিৎসকের সাথে আলোচনা করুন। কোন বিষয় বুঝতে অসুবিধা হলে কিংবা আরও তথ্য জানতে চাইলে দায়িত্বরত চিকিৎসককে গবেষণা সম্পর্কিত প্রশ্ন করতে পারেন। মনে রাখবেন আপনার অংশগ্রহণ আপনার বর্তমান চিকিৎসা ব্যবস্থায় কোন প্রভাব ফেলবে না। যদি আপনি গবেষণাতে অংশগ্রহণ করতে চান তাহলে আপনাকে রোগীর তথ্য ও সম্মতিপত্র পূরণ স্বাক্ষর এবং তারিখ সহ পূরণ করতে হবে। একইসাথে ফরমটি আপনাকে সংরক্ষণ করে রাখতে হবে, কারণ এখানে গবেষণা বিষয়ক গুরুত্বপূর্ণ তথ্য এবং চিকিৎসকের ফোন নম্বর রয়েছে।

**গবেষণার উদ্দেশ্য:** উচ্চরক্তচাপের রোগী, যাদের বয়স ৫৫ বছরের বেশী এবং যারা চিকিৎসা নিয়েছেন কিন্তু রক্তচাপ নিয়ন্ত্রণে নেই, তাদের উপর অ্যামলোডিপিন এবং ইন্ডাপামাইড সিমিতি ডোজের কার্যকারিতা এবং সহনশীলতা দেখা।

**ঔষধের তথ্য:** ঔষধটি বাংলাদেশের স্বাস্থ্য অধিদপ্তর থেকে নিবন্ধিত।

**অংশগ্রহণকারী:** বর্তমান গবেষণাটিতে ২৫০ জন রোগীকে স্বচ্ছন্দুক্ত করার পরিকল্পনা নেওয়া হয়েছে। আপনার চিকিৎসক যদি মনে করেন আপনার অনুরোধ চিকিৎসার জন্য NATRIXAM® প্রয়োজন, তাহলে আপনি গবেষণাতে অংশগ্রহণ করতে পারবেন। গবেষণাতে অংশগ্রহণের পর চাইলে যে কোন সময় আপনি তা বন্ধ করতে পারবেন। এই ক্ষেত্রে বর্তমানে চিকিৎসক আপনার নিয়ত থাকার কারণ জিজ্ঞাসা করতে পারেন। গবেষণায় আপনার অংশগ্রহণ, আপনার মানসম্মত স্বাস্থ্যসেবা পাওয়ার ক্ষেত্রে কোন প্রভাব ফেলবে না।

**গবেষণার পদ্ধতি:** এই গবেষণার চিকিৎসা সংক্রান্ত তথ্যাদি ১২ সপ্তাহের জন্য সংরক্ষণ করা হবে। গবেষণা চলাকালীন সময়ে আপনার সম্পর্কে চিকিৎসক নিম্নু তথ্য নিয়ে যার মধ্যে রয়েছে আপনার বয়স, অসুখের বিবরণ, বর্তমান অবস্থা এবং অন্যান্য অসুখ। আপনার সাথে যোগাযোগের জন্য চিকিৎসক আপনার যোগাযোগের যাবতীয় তথ্যাদি জেনে নিবেন।

**রোগীর দায়িত্ব ও কর্তব্য:** গবেষণায় অংশগ্রহণের জন্য আপনার নৈমন্দিন কাজের কোন পরিবর্তন হবে না কিংবা কোন নীতিমালা থাকবে না। আপনার চিকিৎসক যে ঔষধগুলো নেবেন করতে দিয়েছেন সেগুলো চালিয়ে যাবেন এবং প্রয়োজনীয় পরীক্ষা ও পরামর্শের জন্য চিকিৎসকের কাছে নিয়মমত যাবেন। ওষুধের কোন পার্শ্বপ্রতিক্রিয়া পরিলক্ষিত হলে গবেষণা চলাকালীন সময়ে চিকিৎসককে অবহিত করবেন।

**তথ্যের ব্যবস্থাপনা (গবেষণা চলাকালীন):** এই গবেষণা চলাকালীন সময়ে আপনার চিকিৎসক আপনার কাছ থেকে নিয়মিত তথ্য সংগ্রহ করবেন। আপনি যদি মনে করেন গবেষণায় অংশগ্রহণ করবেন না তাহলে দায়িত্বরত চিকিৎসককে অবহিত করবেন।

**গোপনীয়তা রক্ষা:** আপনি যদি গবেষণাতে অংশগ্রহণ করতে ইচ্ছুক হোন তাহলে আপনার যাবতীয় ব্যক্তিগত তথ্যাদি গোপন রাখা হবে। কেবলমাত্র কর্তৃপক্ষের কাছে সেবাদানের জন্য বেশকী করলে এ ব্যক্তিগত তথ্য ব্যবহার করা হতে পারে।

**গবেষণার ফলাফল:** গবেষণাটির গবেষণার তথ্য এবং ফলাফল স্বাস্থ্যবিষয়ক পত্রিকা কিংবা সেমিনারে তথ্য আকারে প্রকাশিত হবে। কিন্তু আপনার নাম কিংবা অন্যান্য ব্যক্তিগত তথ্য সেখানে উল্লেখ করা হবে না।

**প্রশ্নের উত্তরের জন্য যোগাযোগ:** আপনার যদি গবেষণার ধরণ কিংবা ঔষধ নিয়ে গবেষণা চলাকালীন সময়ে কোন প্রশ্ন থাকে, দয়া করে আপনার চিকিৎসকের সাথে যোগাযোগ করবেন।

ফোন /টেলিফোন নম্বর:.....

তথ্যগুলো পড়ার জন্য আপনাকে ধন্যবাদ।

Patient consent form

COMBINE trial

# Evaluation criteria

## Main efficacy criteria

- Supine office SBP/DBP (mmHg) and Standing SBP/DBP (change from baseline to W12 post-baseline value achieved in W0-W12 period)
- BP normalization corresponding to the percentage of patients with SBP < 140 mmHg and DBP < 90 mmHg
- Response to treatment rates defined as SBP < 140 mmHg and DBP < 90 mmHg and/or SBP decrease ≥ 20 mmHg from baseline and/or DBP decrease ≥ 10 mmHg from baseline

# Evaluation criteria

## Secondary criteria

- Changes in pulse BP and visual scale
- Assessment in efficacy and tolerability in doctors and patients' opinion

## Safety criteria

- Laboratory investigations (Potassium, Sodium, Creatinine, HbA1c, eGFR, Cholesterol, LDLC/HDLC, Triglycerides
- Adverse events

COMBINE trial

# Study Chart/Gantt Chart

| | Visit 1 (inclusion) | Visit 2 (2 weeks) | Visit 3 (1 month) | Visit 4 (3 months) |
|---|---|---|---|---|
| Inclusion of patients according to inclusion / exclusion criteria | X | | | |
| Signing the patient's informed consent form | X | | | |
| Recording of epidemiological characteristics of patients | X | | | |
| Recording of current therapy | X | | | |
| Recording of therapy after its addition or changing | X | X | X | X |
| Recording of the prescribed dose of NATRIXAM during therapy | X | X | X | X |
| BP and HR in the sitting and standing positions | X | X | X | X |
| Assessment of well-being by VAS | X | X | X | X |
| Assessment if the treatment efficacy and tolerability by doctor and by patient | | | | X |
| Assessment of adverse events | | X | X | X |
| Filling out the self-control diaries of BP by patients before visits to the doctor | | X | X | X |
| Laboratory tests (creatinine +clearance, potassium, sodium, glucose, uric acid, lipid spectrum, ALT, and AST) | X | | | X |

COMBINE trial

# Laboratory investigations

| Investigations |
| --- |
| Potassium |
| Sodium |
| HbA1c |
| Creatinine |
| eGFR |
| Total cholesterol |
| LDL-C |
| HDL-C |
| Triglycerides |

COMBINE trial

# Case report forms

## Informed consent of the patient

## (To be kept by the doctor)

**INFORMED CONSENT OF THE PATIENT**

Hereby, I (surname, first name and patronymic name)

_____

confirm my consent to participate in the

OPEN MULTICENTER OBSERVATIONAL PROGRAM "NATRIXAM".

I got an explanation about the purpose of program and action of the drug used.

I am informed that within 3 months I will need to visit the clinic _____ at least 4 times, to see the doctor _____, and to perform the necessary examinations.

I understand that at any time I can stop participation in the program, and this will not affect my further treatment.

I am informed of a need to comply with the prescribed diet and exercise regimen, as well as the regimen of taking the drug.

The doctor _____, who discussed with me the question of my participation in this observational study, gave me an exhaustive explanation of the nature, purposes and duration of the study. I had the opportunity to ask him/her questions about all aspects of this observational study, and I was told the name of the person to whom I can apply for any questions arising during the study.

After due consideration, I agree to cooperate with the doctor responsible for the observational program and, if necessary, with all persons authorized by him/her. I will immediately inform them of any changes in my state of health.

Signature of the patient _____ Date ____ | ____ | _____

Doctor (surname, first name and patronymic name)

_____

Signature of the doctor _____ Date ____ | ____ | _____

## Informed consent of the patient

## (To be provided to the patient)

**INFORMED CONSENT OF THE PATIENT**

Hereby, I (surname, first name, and patronymic name)

_____

confirm my consent to participate in the

OPEN MULTICENTER OBSERVATIONAL PROGRAM "NATRIXAM".

I got an explanation about the purpose of program and action of the drug used.

I am informed that within 3 months I will need to visit the clinic _____ at least 4 times, to see the doctor _____, and to perform the necessary examinations.

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The doctor _____, who discussed with me the question of my participation in this observational study, gave me an exhaustive explanation of the nature, purposes and duration of the study. I had the opportunity to ask him/her questions about all aspects of this observational study, and I was told the name of the person to whom I can apply for any questions arising during the study.

After due consideration, I agree to cooperate with the doctor responsible for the observational program and, if necessary, with all persons authorized by him/her. I will immediately inform them of any changes in my state of health.

Signature of a patient _____ Date ____ | ____ | _____

Doctor (surname, first name, and patronymic name)

_____

Signature of a doctor _____ Date ____ | ____ | _____

COMBINE trial

# Final status after completion

| Target sample | Enrolled patient |
| --- | --- |
| 250 | 213 |

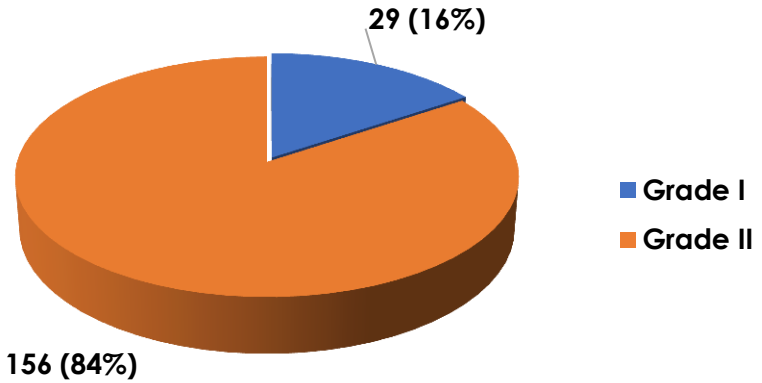
| 4th visit (Except investigation) | 4th visit (With investigation) |
| --- | --- |
| 185 | 116 |

COMBINE trial

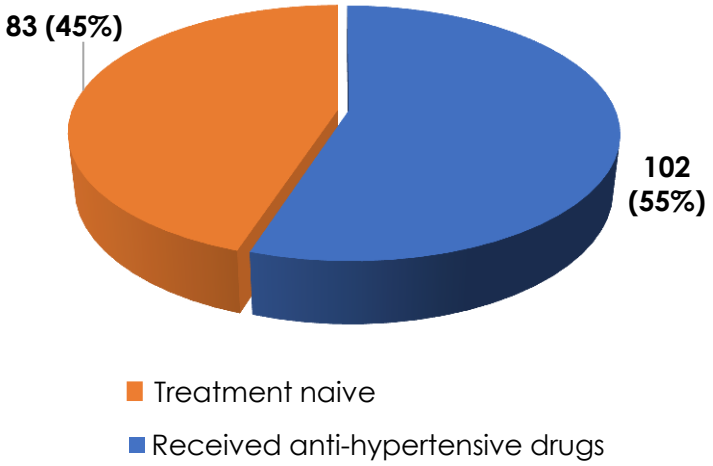
# Baseline Characteristics

| Variables | Frequency | (%) |
|---|---|---|
| Sex | | |
| Men | 76 | 41.1 |
| Women | 109 | 58.9 |
| Age (years) | | |
| 55–59 years | 84 | 45.4 |
| 60–69 years | 63 | 34.1 |
| 70–79 years | 30 | 16.2 |
| ≥ 80 years | 8 | 4.3 |
| Mean ± SD<br>Range (min-max) | 62.4±7.4<br>(55-85) years | |
| Risk factors | | |
| Current smoker | 26 | 14.1 |
| Dyslipidemia | 62 | 33.5 |
| Fasting plasma glucose ≥ 5.6 mmol/L | 54 | 29.2 |
| Abdominal obesity | 71 | 38.4 |
| Family history of CVD | 21 | 11.1 |
| Concomitant diseases and conditions | | |
| Confirmed LVH | 6 | 3.2 |
| Proteinuria | 8 | 4.3 |
| CAD | 7 | 3.8 |
| Stable angina | 8 | 4.3 |
| History of myocardial infarction | 5 | 2.7 |
| History of coronary revascularization | 2 | 1.1 |
| History of stroke or TIA | 6 | 3.2 |
| Peripheral artery disease | 1 | 0.5 |
| Class I or II CHF | 0 | 0.0 |
| Type 2 diabetes mellitus | 74 | 40.0 |
| COPD/asthma | 27 | 14.6 |

# Distribution of hypertensive patients




By grade




By receiving medication

COMBINE trial

# Result

# Efficacy: Rapid & powerful BP reduction

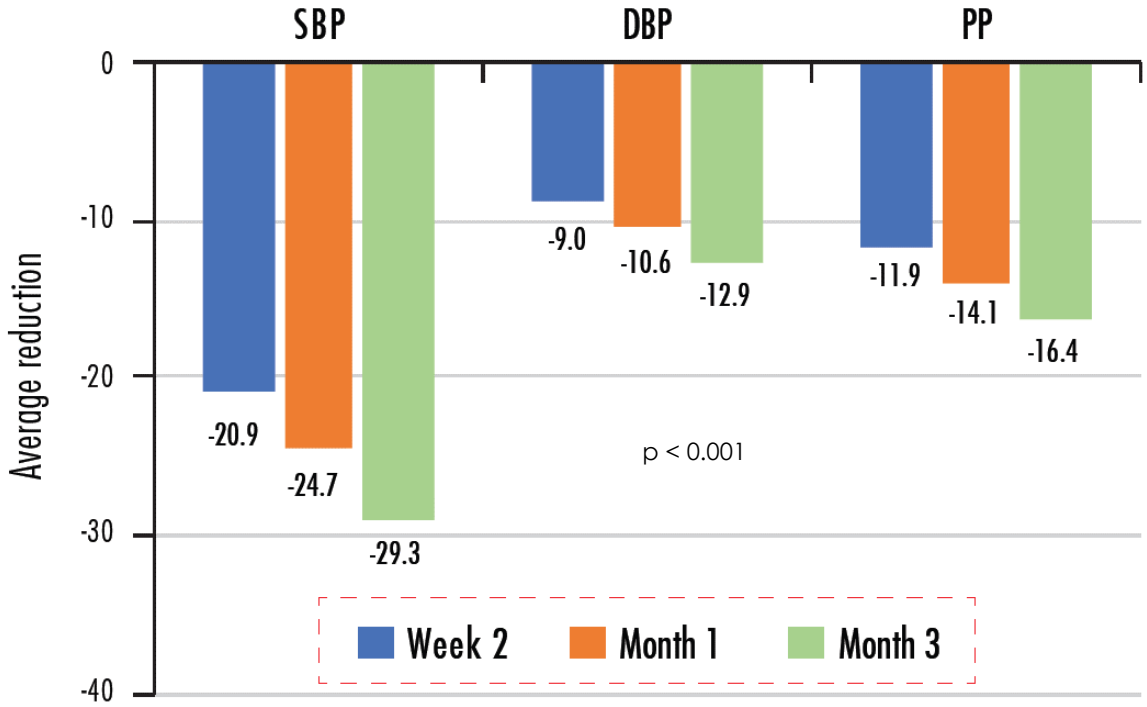



Fig: Changes of blood pressure during the study period (n=185)

COMBINE trial

# Efficacy: 9 out of 10 patients are controlled after treatment

| Follow up | SBP | Number of patients | Percentage |
|---|---|---|---|
| **After 2 weeks** | <140 mmHg | 113 | **61%** |
| **After 1 month** | <140 mmHg | 142 | **77%** |
| **After 3 months** | <140 mmHg | 164 | **89%** |

**Table: Distribution of the hypertensive patients by SBP reduction <140 mmHg in follow up**

COMBINE trial

# Efficacy: Effective systolic blood pressure reduction

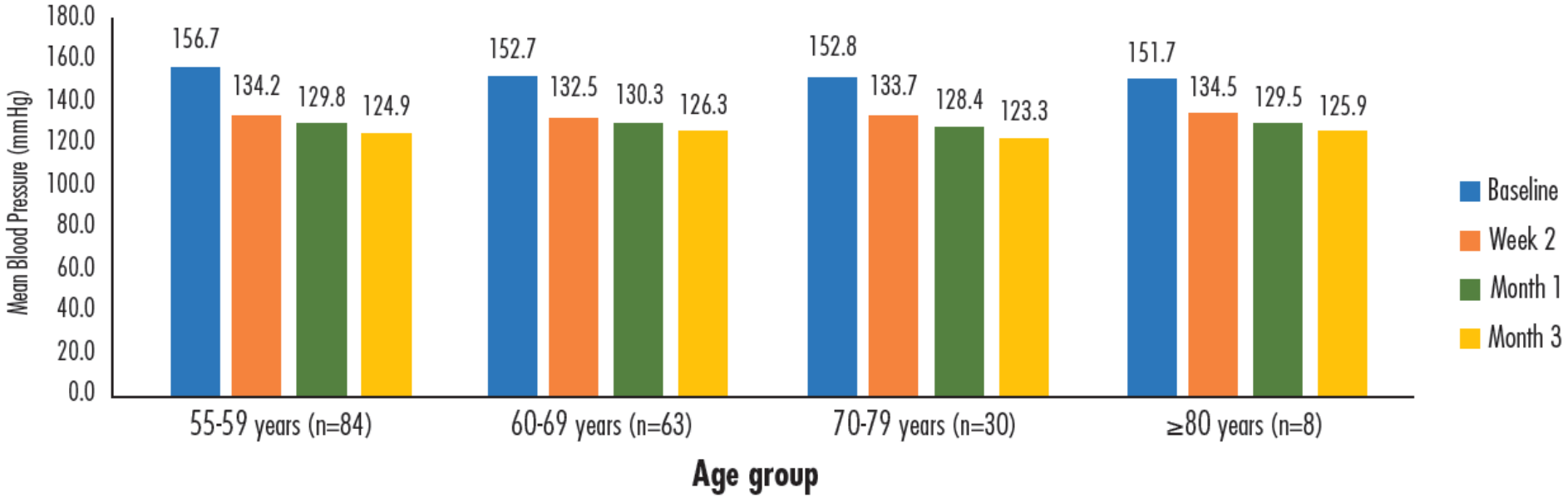



**Fig: Changes in mean systolic blood pressure (SBP) during the treatment in different age groups**

# Tolerability: Almost neutral with lesser side effects

| Variables | Baseline Mean ± SD | After 3 months Mean ± SD | Difference Mean ± SD | p-value (n=116) |
|---|---|---|---|---|
| S. creatinine | 1.01 ± 0.27 | 1.03 ± 0.26 | 0.02 ± 0.22 | 0.213 |
| Sodium | 137.9 ± 3.42 | 137.5 ± 3.17 | 0.40 ± 4.27 | 0.312 |
| Potassium | 4.05 ± 0.54 | 3.87 ± 0.51 | 0.18 ± 0.58 | 0.002 |

| Side effects | % |
|---|---|
| Leg edema | 1.6% |
| Electrolyte Imbalance | 2% |
| Muscle cramp/abdominal pain | 1% |
| Sudden Fall of BP | 0.5% |

# Improved well being of the patient

| Variables | VAS Mean±SD | Difference Mean±SD | % changes | p-value |
|---|---|---|---|---|
| **Visit 1** | 55.87 ± 17.04 | - | - | |
| **Visit 2** | 68.19 ± 14.53 | 12.32 ± 14.58 | 22.1% | <0.001 |
| **Visit 3** | 72.74 ± 14.57 | 16.86 ± 18.57 | 30.2% | <0.001 |
| **Visit 4** | 78.89 ± 14.05 | 23.02 ± 20.64 | 41.2% | <0.001 |

**Table: Comparison of VAS from visit 1 with visit 2, visit 3 and visit 4 (n=185)**

# Disclosure

- The **COMBINE** trial was supported by SERVIER
- Patients were given Tab. **NATRIXAM** which was launched by SERVIER, comprised of original Indapamide (Servier) and original Amlodipine (Pfizer)

# Take home message

- Hypertension is a real threat and elderly populations are at higher risk
- There is scarcity of clinical data regarding hypertension treatment in Bangladeshi population
- The **COMBINE** trial was conducted to evaluate the efficacy and tolerability of fixed dose combination of amlodipine and indapamide over hypertensive patients > 55 years of age
- **Amlodipine-Indapamide combination** is found to be effective and well tolerated for Bangladeshi hypertensive patients

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# Thank you