

Original research article

# Risk of dementia in patients taking diuretics as antihypertensive treatment in a tertiary care teaching hospital at Kerala: A cross-sectional study

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## Abstract

**Background:** Hypertension is considered to be the third most important disease in the list of diseases in South Asian region. Several trials have shown active treatment of hypertension reduced the risk of dementia. This study was adopted to understand the risk of dementia in patients using diuretics as antihypertensives for a period of one and half year.

**Materials and Methods:** This study was conducted among hypertensive patients of age group 55-65 years taking diuretics as antihypertensive medication. Detailed history of hypertension and mental illness is taken.

**Results:** In glimpse, 16% of the study population scored complete score of 30 in MMSE test. Majority i.e. 34% of population obtained a score of 29. Men had a higher deviation compared to women for frusemide, torsemide and indopamide. Women had a higher standard deviation compared to men for aldactone and chlorthalidone. Hydrochlorothiazide had an equal standard deviation for men and women.

**Conclusion:** As the score of the person decreases, he/she has an increased possibility to end up with cognition defect. Majority of study population scored between 25 to 30 and have less risk to develop dementia.

**Keywords:** Diuretics, hypertension, dementia

## Introduction

India is experiencing a rapid health transition with a larger and rising burden of chronic non-communicable diseases like hypertension, diabetes, cardiovascular diseases, stroke, cancer, and chronic lung diseases. Hypertension exerts a substantial public health burden on cardiovascular health status and health care systems in India. It is directly responsible for 57% of all stroke deaths and 24% of all coronary artery disease deaths in India. The WHO rates hypertension as one of the most important causes of premature death worldwide. About 33% of the urban population and 25% of the rural population in India are hypertensive. Of these only 25% of the rural population and 42% of the urban population are aware of their hypertensive status. And only 25% of the rural and 38% of the urban population are being treated for hypertension. In 2005, a study determined that 20.6% of Indian men and 20.9% of Indian women suffered from hypertension<sup>[1]</sup>. According to WHO studies, the percentage of Indian men suffering from hypertension had gone up to 33.2% in men and 31.7% in women. In total, the prevalence of hypertension in India was 32.5%<sup>[2]</sup>.

Dementia is a syndrome in which there is a deterioration of memory, thinking, behavior, and an inability to perform everyday activities. Although dementia mainly affects old people, it is not a normal part of aging. Worldwide around 50 million people have dementia and there are nearly 10 million new cases every year. It is one of the major causes of disability and dependency among old people worldwide.

Considering the prevalence of hypertension and dementia in India, it has become essential to understand the relationship between dementia and hypertensive patients on treatment in the age group of

55-65 years.

A cross-sectional study is taken by grouping them based on the type of medication they are treated and an MMSE test will be carried out along with a cognitive ability test to arrive at a reasonable conclusion based on existing standards. The result of the study can be a good database for the clinicians to opt for suitable medicines that can prevent complications and early onset of dementia.

**Literature review**

Recent world Alzheimer's report indicates that 47 million people worldwide are living with dementia today and it is expected to increase to 75 million members by 2030<sup>[3]</sup>. The trend can increase up to 132 million by 2050<sup>[4]</sup>.

Prince *et al.*, have inducted that 68% of Alzheimer's cases are from low and middle-income countries. He also pointed out that the impact is high with old age members. He also has indicated that in developing countries the high burden of uncontrolled hypertension was detected (of about 31.6%), a common finding among older adults residing in developing countries and is expected to increase due to ongoing health transitions<sup>[5]</sup>.

The Sys-Eur trial which started in 1988 showed that the active treatment of hypertension reduced the incidence of dementia by 50%. It reduced from 7.7 to 3.3 cases per 1000 patient-years. It was found that antihypertensive treatment in the elderly population having isolated systemic hypertension reduced the incidence of dementia<sup>[6]</sup>. In this study, the drug Nitrendipine was taken as first-line medication. If necessary the drug was replaced by Enalapril as a second-line drug and or Hydrochlorothiazide as a third-line drug.

Ertekinet *al.*, have indicated that health-related factors such as a family history of having Dementia, Parkinson's disease, and heart disease have also been associated with dementia occurrence at a later part of life. They also have indicated that increasing age, members from low socio-economic status, poor education, and members from rural areas are associated with a high risk of dementia<sup>[7]</sup>.

Analysis of dementia studies in the age group 55-65 years in India is scanty and hence a methodical study is required to provide a good database to clinicians who treat the patients to understand its influence on the rate of reduction of dementia. Thus this study is of national importance.

The medical research council's treatment trial of hypertension project did not show any difference in a neuropsychiatric test result in the 54-month long project. The drugs taken into account were beta-blockers with or without diuretics. A similar study –‘Systolic hypertension in the elderly program’ also did not get any major results regarding the effect of antihypertensive medications in preventing the onset of dementia.

Perindopril protection against recurrent stroke study showed a positive result. Perindopril and Indapamide were the drugs utilized in the study. This study was to determine the benefit of antihypertensive treatment among patients with a history of stroke. It was seen that there was a 19% decline in the risk of cognitive impairment when they were reviewed after 4 years<sup>[8]</sup>.

EdwincK.Tan *et al.*, have indicated that antihypertensive medication with older patients indicated a reduced level of dementia<sup>[9]</sup>. Hence, it is essential to understand the effects of Diuretics through a controlled experimental study.

Heart outcome prevention evaluation (HOPE) study shows that a 41% decline in cognitive impairment was seen when reviewed after 4.5 years. ACE inhibitors in Taipei showed that angiotensin receptor blockers are much better in preventing dementia than ACE inhibitors, but both drugs can prevent the early onset of dementia<sup>[10]</sup>.

Having known all these, a methodical case study was adopted to understand the status of patients using diuretics for hypertension for a period of one year.

**Mechanism of action of diuretics**

Diuretics have been the standard antihypertensive drugs over the past four decades though they do not lower BP in normotensives

Diuretics	Mechanism of action	Side effect
Loop diuretic	Loop diuretics act on the thick ascending loop of henle and inhibit the $na^+ k^+ 2cl^-$ cotransport. It also has weak carbonic anhydrase inhibitory action.	It is dose-dependent and includes hyponatremia, hypokalemia, metabolic alkalosis, hypovolemia, hypotension, and to a lesser extend hyperuricemia, hypocalcemia, hypomagnesemia, Hyperglycemia, hyperlipidemia, urinary urgency and

		impotence.
Thiazides	Thiazide diuretic inhibits the $Na^+Cl^-$ symporter	Hyponatremia, hypokalemia, hypomagnesemia, hypocalcemia, metabolic acidosis, hypovolemia, hypotension, hyperglycemia, hyperlipidemia, and impotence.
Potassium sparing diuretic	Spironolactone is an aldosterone antagonist which acts by preventing aldosterone from combining with an intracellular mineralocorticoid receptor (mr) and induces the formation of aldosterone-induced protein. This promotes the secretion of sodium but retains potassium.	Hyperkalemia is one of the major side effects due to the retention of potassium by the drug. Other side effects are decreased libido, impotence, gynecomastia, and metabolic acidosis. Sexual side effects in spironolactone are mainly due to inhibition of attachment of dihydro-testosterone to the androgen receptor.

**Aims and Objectives of the research project**

The study aims to provide a good database to clinicians to understand the risk of dementia in patients taking diuretics as antihypertensive treatment in the age group of 55-65 years, by carrying out a methodical study.

The study is conducted in a period of two years (February 2020- February2022) in 500 patients in a tertiary care centre in Palakkad, Kerala.

**Material and Methods**

**Methodology and Research design**

- Approval to conduct the study will be obtained from an institutional ethics committee.
- Patients who are eligible to take part in the study will be invited.
- Proper explanation regarding the nature of the study will be given and the patient is given the choice of taking part in the study.
- Patients willing to take part are made to give written informed consent.
- A detailed history of hypertension and mental illness is taken.
- The patient is made to take the MMSE test. Assistance will be provided when required in case of any language barrier.
- The results will be tabulated and will be analyzed statistically.

**Inclusion criteria**

- Patients between 55-65 years who are suffering from hypertension and taking diuretics as antihypertensive medication.
- The patient must take antihypertensive medication for one year.

**Exclusion criteria**

- Normotensive patients.
- Hypertensive patients who are not in the 55-65 years age group.
- Hypertensive patients who are taking antihypertensive drugs other than diuretics.
- Patients already diagnosed with dementia or have a family history of dementia.
- Patients who have other mental illnesses.
- Patients who are not willing to take part in the study.

**Sample size, sampling technique and statistical analysis**

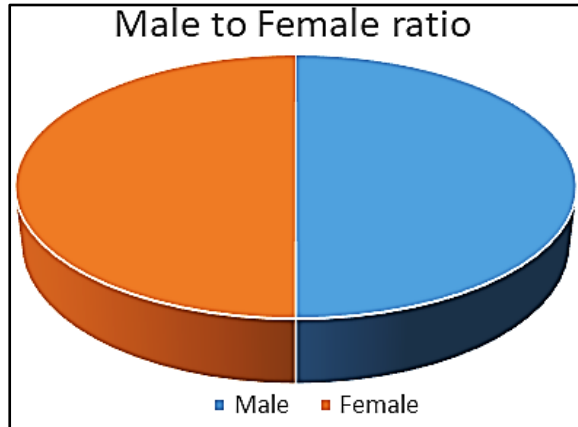
- **Study design:** prospective case control study
- **Randomization:** not randomized
- **Sample size:** 500 patients
- **Study duration:** two years
- Potential risks and benefits
- There are no risks.

**Benefits of the study:**

- Understanding the risk of dementia in hypertensive population between 55-65 years
- In advance, necessary lifestyle modifications can be made.

**Results and observations**

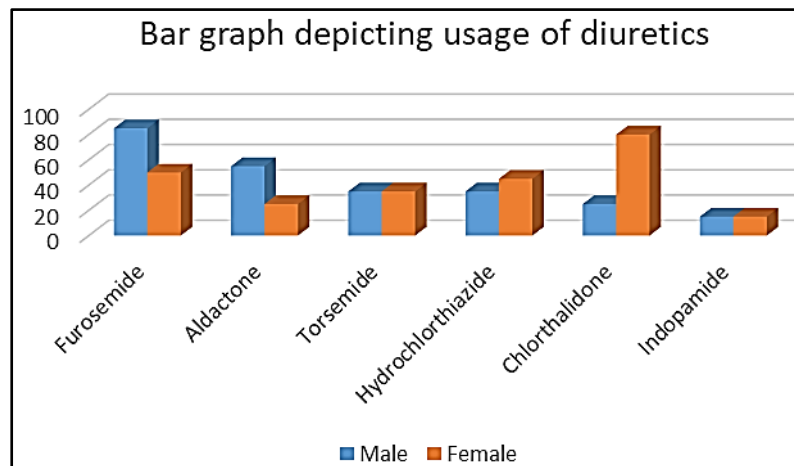
In the study, 500 patients had been using diuretics. It is observed that 250 of them were male and the other 250 were female.



**Fig 1:** Ratio between Males and Females that have participated in the study

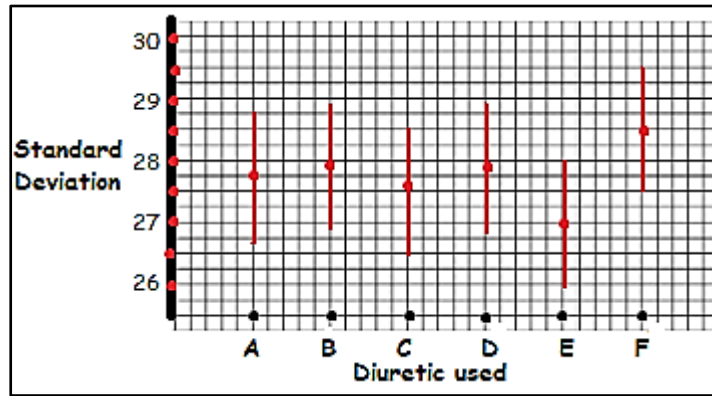
Out of the 500 patients taking diuretics, 80 patients have obtained a score of 30 which is 16% of the population. The maximum number of patients taking diuretics have obtained a score of 29. 170 out of 500 patients taking diuretics have obtained a score of 29. This shows that 34% of the study population taking diuretics have obtained a score of 29. Among the diuretics users, 75 patients out of 500 have taken a score of 28 which is 15% of the population. 135 patients have obtained a score of 27. 38 out of 500 diuretic users have obtained a score of 26. The average score of patients using diuretics is 28.23077.

Of the 500 participants in the study, 85 men and 50 males used Furosemide. Aldactone was used by 55 males and 25 females. Torsemide was used by 35 men and 35 women. Of the 500 participants, Hydrochlorothiazide was used by 35 men and 45 females. Chlorthalidone was used by 25 men and 80 women in the study. Out of the 500 participants, Indapamide was used by 15 men and 15 women. Figure 2 indicates the usage of each diuretic by males and females in the study.



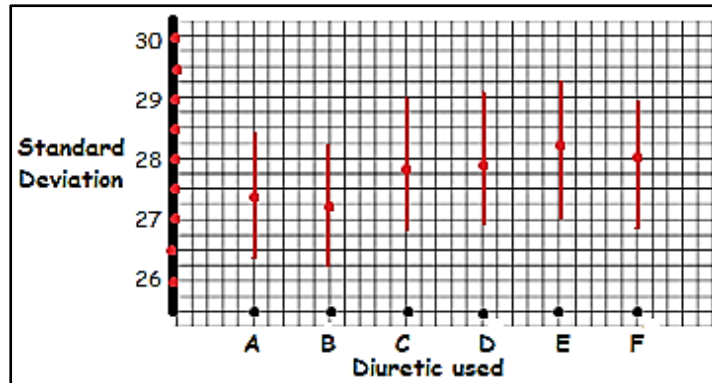
**Fig 2:** Diuretic used by participants according to sex.

In men, the standard deviation indicate was the highest for Indapamide which was 28.5. Both Torsemide and Hydrochlorothiazide had the next highest standard deviation indicated of 27.9. Furosemide had the next highest standard deviation indicated of 27.8 in men. Aldactone had a standard deviation indicate of 27.6, while Chlorthalidone had a standard deviation of 27.1 in men.



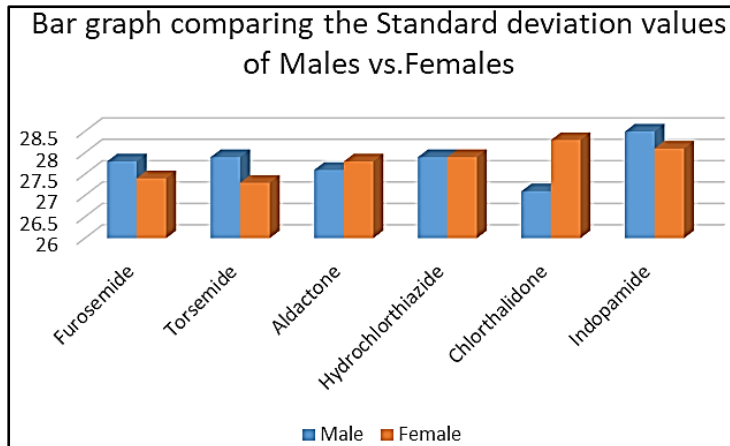
**Fig 4:** Variation in the standard deviation indicates for men for **A)** Furosemide **B)**Torseamide**C)**Aldactone**D)**Hydrochlorothiazide **E)**Chlorthalidone**F)**Indopamide

In women, the standard deviation indicated was seen to be the highest for Chlorthalidone with 28.3. Indapamide had the next highest indicate in females with 28.1. Hydrochlorothiazide had a standard deviation indicate of 27.9. Aldactone was seen to have a standard deviation indicate of 27.8. Furosemide had a standard indicator of 27.4 in women, while Torseamide had a standard deviation indicate of 27.3.



**Fig: 5** shows the variation in standard deviation indicated for women for **A)** Furosemide **B)**Torseamide**C)**Aldactone**D)**Hydrochlorothiazide **E)**Chlorthalidone**F)**Indapamide

Men had a higher standard deviation compared to women for Furosemide, Torseamide, and Indapamide. Women had a higher standard deviation compared to men for Aldactone and Chlorthalidone. Hydrochlorothiazide had an equal standard deviation for men and women.



**Fig 3:** Bar graph comparing the standard deviation of Males and Females**Discussion**

According to the ICD-10 classification of Mental and Behavioral Disorders, dementia is a type of disorder, a progressive decline in memory, learning, orientation, language, comprehension, and judgement<sup>[10]</sup>. This causes a health problem with a substantial economic impact. Thus a methodical questionnaire was prepared to acquire complete data to accrue important conclusions. Based on the scores, the degree of impairment is either questionably significant, mild, moderate, or severe. The degree of impairment is considered questionably significant when the score is between 25 and 30. Such people may have clinically significant but mild deficits. There is a chance of disturbance only in the most demanding activities of day-to-day life. When the score is between 20 and 25, the person is said to have mild impairment. Such people might require some assistance in daily life along with supervision and support. If the score is between 10 and 20, the person is said to have a moderate degree of impairment and may need 24-hour supervision. When the score is in-between 0 to 10, they are said to have severe impairment and would mostly not be testable. In the present study, the details related to genetic factors, glycemic data or the actual blood pressure, smoking or alcohol intake, and the level of education and baseline cognitive functioning, which are needed to be considered in detail. Since the study was carried out where the number of patients approach the hospital from villages, the complete data analysis got restricted.

In the study conducted in Taipei by Ye-Chun Kuan et.al, it is seen that angiotensin receptor blockers have a higher ability to reduce the onset of dementia than ACE inhibitors. A 40% reduction in risk is obtained from angiotensin receptor blockers compared to 26% obtained from ACE inhibitors.

In the study conducted by the Medical Research Council (MRC) among 2584 elderly subjects over 54 months, no significant result was found in the neuropsychiatric test done among the group treated with beta-blockers, the group treated with diuretics, and the placebo group. In the Systolic Hypertension in the Elderly Program (SHEP) study, there was no significant result among the group taking diuretics, the group taking beta-blockers, and the placebo group, although the risk was lower in the first group<sup>[11]</sup>. The MRC study and the SHEP study were done in the European zone, where the genetic makeup of the population, habits, and style of living is much different compared to the south Asian region. This study was done to understand the scenario in the South Indian region.

Also, the analysis of results based on comparing the effect of drugs on the dementia risk by considering only a single drug is difficult. In the given population, all patients have obtained scores between 25 and 30. 26% of the female population and 9% of the male population have a perfect score of 30. One woman taking a diuretic, about 20% of the female diuretic using population and 3 men taking diuretics, about 14% of the male diuretic taking population have a perfect score of 30

As the score of the person decreases, he/she has an increased possibility to end up with a cognition defect. The patients who have obtained scores in the lower side of the range have an increased risk of dementia

Than the rest of the study population. Among diuretic users, 8% of the population has obtained a score of 26. This is the fraction of the study population which has obtained a score on the lower end. This fraction of people has an increased risk of getting dementia than the rest of the study population. Among female diuretic users, there isn't any patient who has scored below 28. 6% of the male study population taking diuretics have a score of 25 whereas 10% of the male study population taking diuretics have a score of 26. These are the lowest scores in each category due to which they have the highest risk of dementia within their study category.

Among diuretics, the standard deviation indicates in men are better in spironolactone followed by furosemide and hydrochlorothiazide. Thus in diuretics, spironolactone plays a better role in reducing the risk of dementia.

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