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Research Protocol

Pharmacology Section

Therapeutic Evaluation of Antidiabetic and Antihypertensive Therapy versus Antidiabetic, Antihypertensive and Statins Therapy in the Management of Type 2 Diabetes Mellitus Patients with Hypertension: A Pragmatic Clinical Trial

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ABSTRACT

Introduction: India is grappling with a growing occurrence of Type 2 Diabetes Mellitus (T2DM) and its related conditions, including hypertension and dyslipidaemia, with Cardiovascular Diseases (CVD) being the primary cause of morbidity and mortality. Statins, primarily used for hypercholesterolaemia and CVD prevention, have demonstrated potential in lowering Blood Pressure (BP) through mechanisms that are independent of cholesterol reduction.

Need of the study: Most evidence regarding the effect of statins on BP comes from controlled trial settings, which may not fully reflect real-world scenarios. Additionally, many clinical studies do not compare different therapeutic approaches to evaluate their impact on patients with T2DM and hypertension. This study aims to address this gap by assessing and comparing the effects of different therapies in a more realistic clinical context.

Aim: To assess the real-world effectiveness of adding a statin to an antihypertensive drug compared to an antihypertensive drug alone in patients with T2DM and hypertension.

Materials and Methods: This pragmatic clinical trial will be conducted across three centres from August 2024 to August 2025 in Maharashtra: one tertiary care hospital and two multispecialty private hospitals, namely Shalinitai Meghe Hospital and Research Centre, Nagpur; Hrudaya Cardiac and Vascular Care Centre, Nagpur; and Shri Sai Multispeciality Hospital, Amravati, Maharashtra, India. The study will enroll a minimum of 300 patients who are newly diagnosed with T2DM and hypertension. Patients will be divided into two groups based on the prescriptions given by physicians: Group 1: Antidiabetic drug+Antihypertensive drug+Statins; Group 2: Antidiabetic drug+Antihypertensive drug. Their effects will be assessed on BP, blood sugar and lipid level parameters. Statistical analyses will include linear regression, multiple regression and quantile regression to evaluate the significance of statin therapy on BP control. A p-value <0.05 will be considered statistically significant.

Keywords: Blood pressure, Cardiovascular diseases, Diabetics, Hypercholesterolaemia, Statin drug therapy

INTRODUCTION

India is home to 77 million diabetic patients, making it the second-largest diabetes population in the world, with projections estimating 629 million by 2045 [1,2]. Among these, nearly 90% suffer from T2DM, which has become a predominant cause of death, accounting for approximately 1.7 million deaths annually [1,2]. Recent statistics indicate that 11.4% of the population has diabetes, 35.5% have hypertension, 81.2% suffer from dyslipidaemia, 28.6% are generally obese and 39.5% experience abdominal obesity [3].

Diabetic patients often present with dyslipidaemia, hypertension, chronic kidney disease and a greater risk of CVD mortality and morbidity, making preventative measures crucial [1]. Statins, which are 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, are the approved treatment for hypercholesterolaemia and are a mainstay in preventing primary and secondary CVD in patients with T2DM. Moreover, there is substantial evidence that statins exert myriad biological effects beyond cholesterol lowering, contributing to their ability to prevent cardiovascular events [4].

Several studies have demonstrated that statins significantly lower BP through mechanisms independent of cholesterol reduction, such as improving endothelial function, promoting vasodilation, reducing oxidative stress, decreasing inflammation in the arterial system and down-regulating the angiotensin II type 1 receptor [4-7]. It has been established that statin users are more likely to achieve controlled BP compared to non users among hypertensive patients with a BP of ≥140/90 mmHg [8]. However, this comparison has not been made with dual-drug therapies and most of the available results come from controlled trials, limiting their applicability to real-world settings [4,6,7,9-13]. Therefore, this study aims to assess whether the addition of statins to antihypertensive drugs produces a significant reduction in BP compared to the use of antihypertensive drugs alone in T2DM patients with hypertension.

Objectives of the study:

1. To evaluate the effect of antidiabetic and antihypertensive drugs in the management of patients with T2DM and hypertension.
2. To evaluate the effect of antidiabetic, antihypertensive and statin therapy in the management of patients with T2DM and hypertension.
3. To compare the therapeutic effects of antidiabetic and antihypertensive therapy versus the combination of antidiabetic, antihypertensive and statin therapies in the management of patients with T2DM and hypertension in real-life clinical settings.

REVIEW OF THE LITERATURE

Optimising lipid and BP-lowering therapy in patients with T2DM is recognised as a key strategy to reduce the overall CVD burden [14,15]. Guidelines, such as those from the American College of Cardiology/American Heart Association (2018), recommend the utilisation of statins in diabetic individuals aged 40 to 75 years with Low-Density Lipoprotein Cholesterol (LDL-C) levels between 70-189 mg/dL, without Coronary Artery Disease (CAD) or stroke, as an ideal approach for primary prevention [16]. Similarly, the Malaysian Clinical Practice Guidelines advocate for the use of moderate-intensity statins as primary prophylaxis for all patients aged 40 years and above with T2DM, regardless of their baseline LDL-C levels [17]. For secondary prevention, higher doses of statins are recommended for those with diabetes who also have CAD or elevated CVD risk factors, such as raised LDL-C levels, smoking, or hypertension [14,17].

Despite the strong endorsement by the guidelines and the acknowledged benefits of statins in reducing LDL-C levels and BP, there is documented underutilisation of statins in patients, particularly those over 40 years with T2DM. This underutilisation often results from incomplete adherence to clinical guidelines, lack of awareness of new recommendations and various prescriber-related factors, such as specialty, motivation, concerns about side-effects and patient-related factors [12,18].

To address these issues, a pragmatic clinical trial design will be conducted in routine clinical settings to generate real-world evidence and evaluate the comparative effectiveness of adding statins to antihypertensive medication versus using antihypertensive medication alone in managing BP among patients with T2DM and hypertension. The trial is planned using the Pragmatic Explanatory Continuum Indicator Summary (PRECIS-2) tool, which consists of nine domains, each scoring up to 5 points. This tool ensures that the study aligns with real-world clinical practices, making the results more applicable to everyday healthcare scenarios [19].

By examining real-world trends and comparing the results, this study aims to demonstrate which therapy achieves better control in patients with T2DM and hypertension in real-life clinical settings. The study will assist clinicians in making more informed decisions, optimising treatment strategies and ultimately improving health outcomes for patients with T2DM and hypertension. This initiative is expected to help reduce the burden of diabetes-related complications.

Hypothesis

Alternate hypothesis (H1): The combination therapy of antidiabetic, antihypertensive and statin therapy is more effective in managing T2DM patients with hypertension compared to therapy consisting only of antidiabetic and antihypertensive medications, as measured by improved glycaemic control, BP regulation and cardiovascular outcomes.

Null hypothesis (H0): There is no significant difference in the effectiveness between the combination therapy of antidiabetic, antihypertensive and statin therapy and the therapy consisting of antidiabetic and antihypertensive medications alone in managing T2DM patients with hypertension, in terms of glycaemic control, BP regulation and cardiovascular outcomes.

MATERIALS AND METHODS

This comparative pragmatic clinical trial will assess the effects of adding statins to antihypertensive therapy versus using antihypertensive therapy alone on BP in patients at three outpatient department centres: one tertiary care hospital and two multispecialty private hospitals, over one year, from August 2024 to August 2025. This study will be conducted across three different centres in Maharashtra: one in the Amravati district and two in the Nagpur district.

1. Shalinitai Meghe Hospital and Research Centre, Hingana, Nagpur.
2. Hrudaya Cardiac and Vascular Care Centre, Nagpur.
3. Shri Sai Multispecialty Hospital, Amravati.

This study was approved by the Datta Meghe Institute of Higher Education and Research Ethics Committee (DMIHER (DU)/IEC/2024/325) and is registered in the Clinical Trial Registry of India under the reference number REF/2024/09/092613. The study will be conducted in accordance with ethical guidelines and the principles outlined in the Declaration of Helsinki.

Before the initiation of the study, it is crucial to assess whether the trial is pragmatic or explanatory and to evaluate its feasibility in routine clinical settings. The Datta Meghe Institute of Higher Education and Research Comprehensive Local Research Network Committee appointed three Subject Matter Experts (SMEs) to independently evaluate each domain of the study. To ensure that the study design is both feasible and pragmatic, the SMEs utilised the PRECIS-2 tool [20,21], which assesses trials across nine domains, including recruitment, setting, primary outcomes and other areas to verify alignment with real-world clinical practice.

The study will include a minimum of 100 patients from each centre, resulting in a total of at least 300 participants.

Inclusion criteria:

i. Individuals who are willing to participate in the study and sign an informed consent form.
ii. Patients with newly diagnosed and diagnosed T2DM and hypertension irrespective of dyslipidaemia.
iii. Patients with the BP range: Systolic Blood Pressure (SBP) ≥140 mmHg and/or Diastolic Blood Pressure (DBP) ≥90 mmHg.

Exclusion criteria:

i. Patients who are not willing to participate in the study or to provide informed written consent.
ii. Patients with T2DM.
iii. Patients with a history of hypersensitivity to Hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors.
iv. Pregnant women.

Sample size: The sample size will be calculated using the Daniel Sample Size Formula with the desired margin of error. The sample size formula will be utilised.

$$n=Z^2 P (1-P)/d^2$$

Where,

Z: Statistic for level of confidence- for all level of confidence of 95%, which is convential, Z value=1.96

P: Expected prevalence or proportion of DM [3]=11.4%=0.114

d=error of margin=7%=0.07

Therefore, $n=1.96^2 * 0.114 * (1-0.114)/0.07^2=79$

Overall considering 100 patients in each group from every centre.

Study groups:

Group 1: This group serves as the interventional cohort, including participants who will receive a combination of antidiabetic and antihypertensive medications, along with statins, based on their prescribed treatment regimen.

Group 2: Serving as the control group, participants will be included based on their prescription of a regimen that includes only antidiabetic and antihypertensive medications, without the addition of statins.

The effects of these two major therapies on clinical parameters (BP, BG and lipid profile levels) will be assessed and compared with those observed in Group 1. By thoroughly assessing these domains, the SMEs aimed to ensure that the trial adhered to its pragmatic intent. The SMEs conducted an in-depth evaluation of each domain and assigned scores accordingly, reflecting their commitment to maintaining the study's real-world applicability.

1. **Eligibility criteria:** The study will have a moderately restrictive inclusion criterion, as it will specifically include adult male and female patients with T2DM and hypertension within usual care settings. Given this specificity, a score of 3 is assigned, reflecting a balance between inclusivity and the need for defined patient characteristics.
2. **Recruitment criteria:** Participants will be recruited for this study under usual care conditions, meaning those attending the clinic with the condition of interest will be enrolled without the use of incentives, invitation letters, or other formal recruitment strategies. This pragmatic approach, which mirrors real-world clinical practice, is likely to score a 5 on the PRECIS-2 scale, reflecting a highly practical recruitment method across a diverse range of clinics.
3. **Setting:** This trial will be conducted in identical real-world settings across multiple centres where the researchers intend to apply the results. Such a highly pragmatic approach, replicating everyday clinical environments, is designed to maximise the generalisability of the findings. Therefore, this setting earns a score of 5 points on the PRECIS-2 scale for its real-world applicability.
4. **Organisation:** This trial will require additional resources, including training and instructions for staff on participant enrollment and prescription patterns. Given the need for these extra efforts, but not to an extreme degree, this domain scores a 3 on the PRECIS-2 tool, indicating a moderately pragmatic approach to organisational requirements.
5. **Delivery flexibility:** There will be significant flexibility in how the intervention is delivered, with the specifics left to the discretion of the researcher administering it in usual care settings. This highly pragmatic approach, allowing for real-world variability, scores 5 points on the PRECIS-2 scale, reflecting maximum flexibility in the intervention delivery.
6. **Flexibility in adherence:** No special measures will be required to ensure compliance from study subjects. Routine practices by healthcare professionals, as typically seen in usual care, will be sufficient to manage adherence without compromising flexibility. This highly pragmatic approach earns a score of 5 points on the PRECIS-2 scale, reflecting flexibility in adherence within the usual care framework.
7. **Data collection:** Patient data will be collected during routine follow-ups; however, there may be instances where additional or more frequent data collection is necessary. This balance between routine and occasional intensified data collection reflects a pragmatic study design, earning a score of 4 points in this domain on the PRECIS-2 scale.
8. **Primary outcome:** The primary outcome of this trial is highly relevant from the patient's perspective. It focuses on drug therapies for adults with T2DM and hypertension, specifically measuring the effect of the drug on BP—a parameter routinely monitored in usual care settings. Since no additional laboratory tests will be required to assess this outcome, it scores 5 points on the PRECIS-2 scale, reflecting its pragmatic nature.
9. **Primary analysis:** The data collected in the trial, if analysed on the basis of an Intention-To-Treat (ITT) approach, including all data collected in the analysis, is the most pragmatic in the domain and scores 5 points. If the data analysis excludes the postrandomised non adherent patients and includes only completers, it becomes a highly explanatory trial and scores 1 point in this domain. This method is considered the most pragmatic in this domain, as it reflects real-world scenarios and minimises bias. Therefore, it scores 4 points on the PRECIS-2 scale.

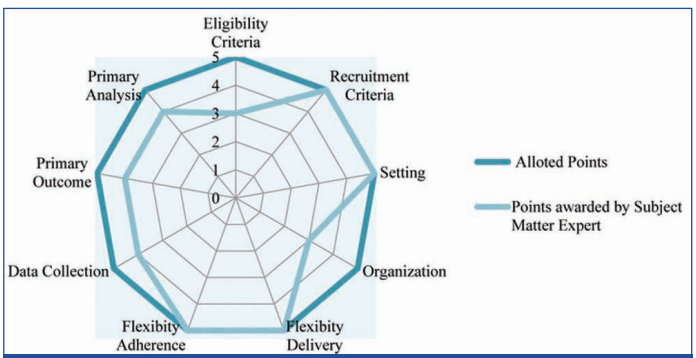
At the start of the study, detailed demographic information—including age, gender, occupation, height, weight, past medical history, comorbidities, and habits—will be recorded in the case report form. Laboratory data will be documented from patients' investigation reports prescribed by their physicians, including Glycated Haemoglobin (HbA1c), fasting and postprandial blood glucose levels, lipid profiles, and additional tests such as liver and kidney function tests. SBP and DBP will be measured using a standardised sphygmomanometer, with measurements taken after the patient has rested for 10 minutes. During each routine visit, as prescribed by the attending physician-typically consisting of three visits or follow-ups-laboratory parameters and BP measurements will be repeated. This approach ensures consistent monitoring of the patient's health status throughout the study [Table/Fig-1].

Assessment	Patient screening	Follow-up		
Informed consent	X			
Demographics	X			
Medical history	X			
Medication	X			
Height	X			
Weight	X			
Vital signs	X	X	X	X
Blood pressure measurements (SBP and DBP)	X	X	X	X
Laboratory tests				
HbA1c	X	X	X	X
FBG	X	X	X	X
PPBG	X	X	X	X
LDL-C	X	X	X	X
Triglycerides	X	X	X	X
HDL-C	X	X	X	X
Additional tests				
Liver function test				
Kidney function test				

[Table/Fig-1]: Monitoring of the patient's health status by various laboratory investigations.

Based on the drug prescriptions advised by the consultant or physician, patients will be divided into two groups. Participants will be scheduled for routine follow-up visits, and during each follow-up, all parameters will be measured. All data from each visit will be documented in an Excel sheet.

By meticulously evaluating all domains, the study achieved a total score of 38 out of 45 points, further confirming its highly pragmatic approach. This score underscores the study's commitment to reflecting real-world clinical practice and ensuring relevant outcomes for patients [Table/Fig-2].



[Table/Fig-2]: PRECIS 2 tool wheel showing points awarded by Subject Matter Expert (SME).

Outcome Measures

Primary outcome: The effect of statins on SBP and DBP from baseline to the end of the study period (three follow-up visits). BP will be measured regularly throughout the study to assess the effect of the different treatment regimens.

Secondary Outcome

Glycaemic control: Changes in glycaemic control will be evaluated from baseline to the end of the study. This will help assess the impact of the regimens on blood sugar management.

Lipid profile: Changes in lipid profile parameters (including total cholesterol, LDL, HDL and triglycerides) will be monitored to evaluate the impact of the inclusion of statins on lipid levels.

Prescription patterns: The study will also analyse the patterns of prescription among two groups, including the frequency, dosage, whether statins are included, the intensity of statins and reasons for the non prescription of statins. This will provide insight into the real-world application of these regimens.

Medication adherence by patients: The consistency of participants in following their prescribed regimens will be monitored, providing insights into the practicality and feasibility of the treatments.

Adverse events: The occurrence and severity of any adverse events will be recorded throughout the study to compare the safety profiles of the regimens.

STATISTICAL ANALYSIS

All data will be accurately documented in a Microsoft Excel spreadsheet. Statistical analysis will be performed to derive insights from the data. Univariate differences between statin users and non users will be assessed by employing simple linear regression. By applying the Wald Test, the relevant statistical significance of these differences will be measured. To evaluate the mean difference in BP between statin users and non users, while adjusting for factors such as age and gender, multiple linear regression incorporating sampling weights will be utilised. Additionally, a quantile regression model will be applied to examine how different quantiles of the BP distribution are influenced by statin use.

REFERENCES

[1] Chandrupatla SG, Khalid I, Muthuluri T, Dantala S, Tavares M. Diabetes and prediabetes prevalence among young and middle-aged adults in India, with an analysis of geographic differences: Findings from the National Family Health Survey. Epidemiol Health. 2020;42:e2020065. Doi: 10.4178/epih.e2020065.

[2] Pradeepa R, Mohan V. Epidemiology of type 2 diabetes in India. Indian J Ophthalmol. 2021;69(11):2932-38.

[3] Anjana RM, Unnikrishnan R, Deepa M, Pradeepa R, Tandon N, Das AK, et al. Metabolic non-communicable disease health report of India: The ICMR-INDIAB national cross-sectional study (ICMR-INDIAB-17). Lancet Diabetes Endocrinol. 2023;11(7):474-89.

[4] Bautista LE. Blood pressure-lowering effects of statins: Who benefits? J Hypertens. 2009;27(7):1478-84.

[5] Bawa S, Dutta S, Varma A, Kumar H, Beg MA, Anjoom M. Comparative evaluation of ACE inhibitors with or without statins in the treatment of essential hypertension in a tertiary care teaching hospital at Dehradun, Uttarakhand. Int J Med Sci Public Health. 2016;5(10):2036-36.

[6] Golomb BA, Dimsdale JE, White HL, Ritchie JB, Criqui MH. Reduction in blood pressure with statins. Arch Intern Med. 2008;168(7):721-27.

[7] Lee S, Yang S, Chang MJ. Anti-hypertensive effects of rosuvastatin in patients with hypertension and dyslipidemia: A systemic review and meta-analysis of randomized studies. PloS One. 2021;16(11):e0260391.

[8] Strazzullo P, Kerry SM, Barbato A, Versiero M, D'Elia L, Cappuccio FP. Do statins reduce blood pressure?: A meta-analysis of randomized, controlled trials. Hypertension. 2007;49(4):792-98. Doi: 10.1161/01.HYP.0000259737.43916.42.

[9] Borghi C, Fogacci F, Agnoletti D, Cicero AFG. Hypertension and dyslipidemia combined therapeutic approaches. High Blood Press Cardiovasc Prev. 2022;29(3):221-30.

[10] Tycinska AM, Janica J, Mroczko B, Musial WJ, Sawicki R, Sobkowicz B, et al. Hypotensive effect of atorvastatin in hypertensive patients: The association among flow-mediated dilation, oxidative stress and endothelial dysfunction. Arch Med Sci. 2011;7(6):955-62.

[11] Abebe RB, Kebede SA, Birarra MK. The association of lipid-lowering therapy and blood pressure control among outpatients with hypertension at the Felege Hiwot Comprehensive Specialized Hospital, Northwest Ethiopia. Front Cardiovasc Med. 2023;10:1071338.

[12] Matthias AT, Kaushalya J, Somathilake G, Garusinghe C. Utilization of statins in patients with type 2 diabetes mellitus: The practice in a lower middle income South Asian country. Int J Diabetes Dev Ctries. 2023;43(3):405-11.

[13] Kanbay M, Yildirir A, Bozbas H, Ulus T, Bilgi M, Muderrisoglu H, et al. Statin therapy helps to control blood pressure levels in hypertensive dyslipidemic patients. Ren Fail. 2005;27(3):297-303.

[14] Elnaem MH, Mohamed MHN, Huri HZ, Azarisman SM, Elkalmi RM. Statin therapy prescribing for patients with Type 2 diabetes mellitus: A review of current evidence and challenges. J Pharm Bioallied Sci. 2017;9(2):80-87.

[15] Kim HL, Kim HM, Kwon CH, Shin JH, Jung MH, Lee CJ, et al. Blood pressure levels and cardiovascular risk according to age in patients with diabetes mellitus: A nationwide population-based cohort study. Cardiovasc Diabetol. 2020;19(1):181.

[16] Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;73(24):3168-3209. Doi: 10.1016/j.jacc.2018.11.002. Erratum in: J Am Coll Cardiol. 2019;73(24):3234-37. Doi: 10.1016/j.jacc.2019.05.012.

[17] MEMS. CPG- Management of Type 2 Diabetes Mellitus (6th Edition) [Internet]. MEMS. 2021 [cited 2024 Oct 14]. Available from: https://mems.my/cpg-management-of-type-2-diabetes-mellitus-6th-edition/.

[18] Mwita JC, Godman B, Esterhuizen TM. Statin prescription among patients with type 2 diabetes in Botswana: Findings and implications. BMC Endocr Disord. 2020;20(1):36.

[19] Jeong NY, Kim SH, Lim E, Choi NK. Pragmatic clinical trials for real-world evidence: Concept and implementation. Cardiovasc Prev Pharmacother. 2020;2(3):85-98.

[20] Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: Designing trials that are fit for purpose. BMJ. 2015;350:h2147.

[21] Norton WE, Loudon K, Chambers DA, Zwarenstein M. Designing provider-focused implementation trials with purpose and intent: introducing the PRECIS-2-PS tool. Implement Sci. 2021;16(1):7. Doi: 10.1186/s13012-020-01075-y.

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