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Study Protocol

PARADISE-PK Study: Prospective assessment of Atherosclerotic Cardiovascular Disease (ASCVD) risk in adults (30 years & above) in Pakistan: A multi-year study investigating incidence, validation, and management strategies.

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Abstract

Background: This study aims to conduct a 10-year follow-up to assess ASCVD risk in Pakistan among individuals aged 30 years and above without a known history of ASCVD. The focus will be on evaluating ASCVD risk over this specific 10-year timeframe. The study will also validate risk assessment scores for identifying high-risk individuals and examine the incidence rate of ASCVD events during long-term follow-up.

Methodology: In this prospective cohort study, ASCVD risk in adults will be assessed by selecting participants aged 30 and above through a non-probability convenient sampling technique. The sample size of 3,513 will be stratified across Pakistan's provinces. Alongside demographics and clinical history, the study will calculate 10-year, 30-year, and lifetime ASCVD risks, incorporating genetic assessment for Apo B. Personalized management recommendations based on ASCVD risk will be provided, and a six-month follow-up will track ASCVD events. The data analysis will employ descriptive statistics and subgroup analysis for comprehensive insights.

Discussion: Given the rising ASCVD prevalence, this study is crucial for understanding disease patterns and identifying high-risk individuals among adults aged 30 and above in Pakistan. It contributes valuable information to the knowledge base on ASCVD, guiding preventive measures for policymakers and healthcare professionals. The ultimate goal is to reduce ASCVD incidence, lessen the burden, and enhance cardiovascular health.

Keywords

ASCVD Risk Assessment, Cardiovascular Disease Prevention, Apo B Genetic Assessment, Public Health Intervention

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Introduction

Cardiovascular diseases (CVD) pose a formidable challenge as the leading cause of premature mortality globally, affecting diverse populations across income societies[1]. The dynamic interplay of sex and age significantly influences the trajectory and prognosis of atherosclerotic cardiovascular diseases (ASCVD)[2,3]. Previously perceived as an ailment predominantly afflicting affluent older men, ASCVD has undergone a transformative shift, emerging as an epidemic impacting the productivity of both young men and women. This resonance is particularly pronounced in communities with varying economic backgrounds, including high-income and low-to-middle-income settings[4]. The far-reaching consequences of premature CVD extend beyond the individual, exerting socioeconomic strains on families and societies, especially in lower-income communities[5]. Recognizing the gravity of this situation, the World Health Organization (WHO) initiated the "25 by 25" campaign, aiming to curtail premature mortality from non-communicable diseases, with over 60% attributed to CVD, by 25% before 2025[6].

While global data on gender- and age-specific variations in CVD risk factors and outcomes have been extensively documented[7,8], the local evidence in Pakistan underscores a crucial research gap. A contemporary ST-elevation acute coronary syndrome (STE-ACS) cohort in Pakistan reveals a noteworthy 12% of premature cases (<40 years)[9]. A study by Ullah et al.[10], comprising 15,106 participants from the Cardiac Registry of Pakistan Catheterization Percutaneous Coronary Intervention, reports 7.4% of patients under 40 years. However, comprehensive local evidence on the incidence of ASCVD among the young population remains scarce.

Current risk assessment guidelines, exemplified by the 2019 ACC/AHA Cardiovascular Risk Assessment Guidelines, predominantly employ race- and sex-specific Pooled Cohort Equations (PCE) for predicting 10-year CVD risk, specifically in adults aged 40 to 75[11,12]. However, these guidelines need more direct applicability to young adults, who often exhibit a paradox of low 10-year ASCVD predicted risk despite harboring a high lifetime risk profile[13]. Acknowledging this discrepancy, the 2018 AHA/ACC cholesterol guideline advocates for estimating lifetime or 30-year ASCVD risk for individuals under 40[14].

Transitioning from risk assessment to lipid modulation, mainly focusing on low-density lipoproteins (LDL), unveils a pivotal role in atherogenesis. LDL assumes primary responsibility in cholesterol transport[15]. The strategic modulation of lipid profiles has emerged as a central goal for cardiovascular prevention, concentrated on mitigating cardiovascular risk through targeted reduction of LDL-cholesterol using diverse lipid-lowering agents. Recent attention has shifted towards compounds offering nuanced insights into pro-atherogenic risk, with apolipoproteins playing an essential role in regulating lipoprotein metabolism and garnering significant attention in atherosclerosis[16].

Among the various apolipoproteins, apolipoprotein B (Apo B) emerges as a crucial component integral to all atherogenic lipids, including very low-density lipoproteins (VLDLs), intermediate-density lipoproteins (IDLs), LDLs, and chylomicrons[17]. Existing literature underscores substantial variability in the lipid composition of Apo B lipoproteins, positioning Apo B as superior to total cholesterol and triglyceride levels in predicting cardiovascular risk[18]. However, the predictive role of Apo B versus LDL-cholesterol remains controversial. While some studies advocate for Apo B as a more precise predictor of cardiovascular risk than LDL-cholesterol and non-high-density lipoprotein cholesterol (non-HDL)[18,19], a recent extensive study involving over 300,000 patients did not establish the superiority of Apo B over LDL-cholesterol in assessing cardiovascular risk[20]. This divergence in findings is mirrored in the 2021 ESC Guidelines on Cardiovascular Disease Prevention in Clinical Practice[21]. Consequently, a series of comprehensive studies is imperative to delineate the precise role of Apo B as a predictor of cardiovascular diseases (CVDs).

In light of Pakistan's escalating ASCVD burden, early identification and optimal management of modifiable risk factors become imperative for prevention. While conclusive studies are lacking, expert recommendations underscore the utility of "total/absolute CVD risk" assessment in guiding management decisions[22]. This study, utilizing the ASCVD risk score and WHO risk score system, aims to evaluate ASCVD risk in young individuals, categorizing risks into low, intermediate, and high groups to guide tailored interventions, be it lifestyle modifications, non-pharmaceutical management, or pharmaceutical interventions, at each specific stage.

Methodology

The objective of this trial

This study aims to conduct a 10-year follow-up to assess atherosclerotic cardiovascular disease (ASCVD) risk among individuals aged 30 years and above in Pakistan without a known history of ASCVD. The primary objective is to evaluate ASCVD risk over this specific 10-year timeframe. The study will also validate risk assessment scores for identifying high-risk individuals and examine the incidence rate of ASCVD events during long-term follow-up.

Study Design

To achieve a comprehensive understanding of ASCVD risk in the adult Pakistani population, this research project will employ a robust prospective cohort study design. This method enables the systematic observation of participants over an extended period, allowing for the identification of potential risk factors and the dynamic evolution of ASCVD risk.

Ethics

Stringent ethical standards will be adhered to throughout the study, aligning with the principles outlined in the declaration of Helsinki. Ethical approval, denoted by Pakistan Medical Association Committee on Ethics (Registration number: AU/098/LKI/12 on 15th April 2024), underscores the commitment to safeguarding participants' rights, privacy, and well-being.

Consent

Informed consent will be obtained from potential trial participants by designated and appropriately trained personnel. Emphasizing the voluntary nature of participation, comprehensive information about the study objectives, potential risks, and benefits will be provided. Additional consent provisions for the collection and use of participant data and biological specimens in ancillary studies, if applicable, will be clearly communicated and obtained.

Confidentiality

To protect confidentiality, stringent measures will be in place for the collection, sharing, and maintenance of personal information about potential and enrolled participants. Data anonymization and secure storage protocols will be implemented before, during, and after the trial. All research personnel involved in data handling will undergo training on confidentiality protocols.

Declaration of Interests

A statement declaring financial and other competing interests for principal investigators for the overall trial and each study site will be provided. Any conflicts of interest will be transparently disclosed, upholding the integrity of the research.

Access to Data

Access to the final trial dataset will be restricted to authorized personnel involved in data analysis and interpretation. Any contractual agreements limiting such access for investigators will be transparently disclosed. The data will be safeguarded to maintain its integrity and protect participant confidentiality.

Study Registration

Transparent research practices will be maintained, as evidenced by the registration of the study's protocol on ClinicalTrials.gov (Registration# NCT06316453). This registration ensures accessibility to the study's detailed protocol, promoting transparency and accountability in research practices. The online availability further facilitates dissemination of information to the broader scientific community.

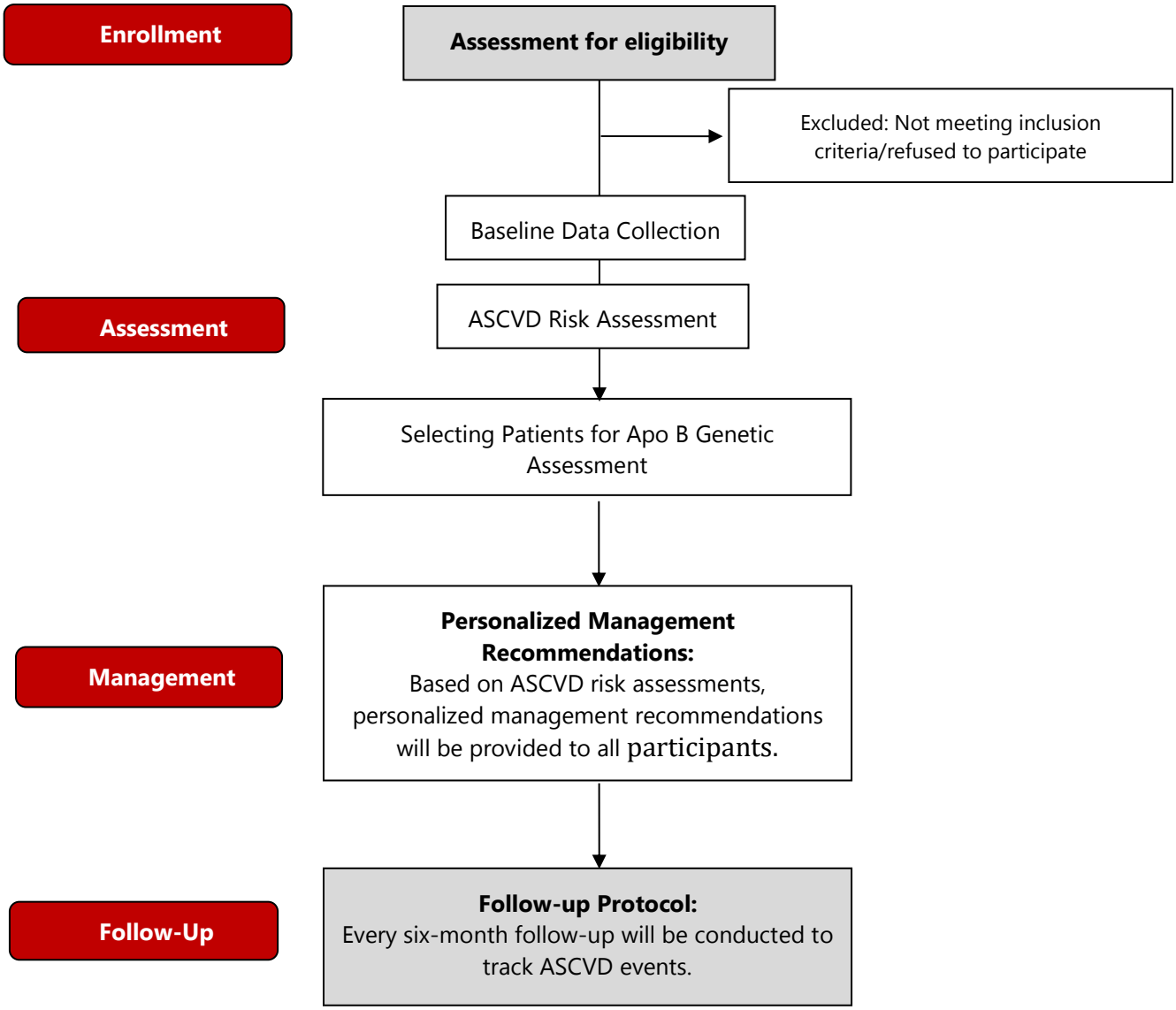

Figure 1: Diagram describing the flow of participants throughout the study

Principle Investigators Selection

The Principal Investigators (PIs) for this study will be carefully selected based on their distinguished expertise in cardiovascular research and affiliation with reputable medical institutions across different provinces in Pakistan. The chosen PIs will demonstrate a comprehensive understanding of ethical considerations, collaborative skills, and leadership qualities essential for overseeing the study's diverse and geographically dispersed components.

Sample Size Calculation

The sample size, determined by insights from a study by An et al.[6], which showcased a median 10-year ASCVD risk of 0.6% in a sizable sample of 414,260 young adults. To enhance the robustness of our study and account for potential observational bias and missing clinical characteristics, the initially identified sample size has been increased by a factor of 1.5. This adjustment ensures a more comprehensive representation, resulting in a final sample size of 3,513 individuals, specifically young and healthy

participants. To accurately reflect the diverse population across Pakistan, stratification based on the 2017 census data will be employed, ensuring representation from all four provinces and optimizing the study's applicability and generalizability.

Participant Selection

To ensure a representative sample reflective of the diverse demographic landscape, we will utilize a deliberate and considered non-probability convenient sampling technique for participant recruitment.

Inclusion criteria

The inclusion criteria will include individuals of any gender aged 30 and above, ensuring a diverse representation to encompass a broad spectrum of experiences and risk factors within this age group. This comprehensive criterion facilitates an in-depth examination of atherosclerotic cardiovascular disease (ASCVD) risk factors, specifically targeting individuals without pre-existing cardiovascular conditions, thereby enhancing the inclusivity of our study.

Exclusion criteria

Exclusion criteria will be applied meticulously, excluding individuals with a confirmed diagnosis of ASCVD or cancer to focus specifically on those without pre-existing cardiovascular conditions. This strategic exclusion ensures a cohort free from confounding factors, enabling a more precise evaluation of ASCVD risk in the chosen demographic. Additionally, participants who express a refusal to provide informed consent will be excluded, prioritizing ethical considerations and respecting individual autonomy in participation. This meticulous approach to participant selection enhances the study's internal validity and strengthens the reliability of the findings.

Recruitment & Assessment Procedures

Efficient and thorough recruitment and assessment procedures will be implemented to ensure the comprehensive examination of ASCVD risk factors among participants.

Participant Recruitment

Participants will be recruited using a deliberate non-probability convenient sampling technique, acknowledging the diverse nature of the population. Informed consent, highlighting the voluntary nature of participation, will be a cornerstone of the recruitment process, fostering ethical and transparent engagement.

Baseline Assessment

A dedicated online portal and proforma will be meticulously employed for baseline data collection. Each participant will be assigned a unique tracking ID, systematically recorded in an online registry. This comprehensive baseline assessment will capture demographic information, clinical history (including hypertension, diabetes, smoking, and positive family history of ischemic heart disease), and key biometric measures (blood pressure, lipid profile, BMI), forming a robust foundation for subsequent analyses.

ASCVD Risk Assessment

Utilizing validated tools such as the Pooled Cohort Equations (PCE) for 10-year ASCVD risk, the 30-year ASCVD risk prediction tool, and lifetime ASCVD risk categories, participants will undergo a thorough risk assessment. This multi-dimensional approach ensures a nuanced understanding of short and long-term cardiovascular risks.

Genetic Risk Assessment

The genetic risk for ApoB will be meticulously assessed by genotyping the APOB rs1042031 variant. Subsequently, the calculation of the genetic risk score (GRS) based on risk alleles will provide a personalized insight into genetic predispositions related to ASCVD risk.

Personalized Management Recommendations

Participants will receive personalized management recommendations derived from the ACC/AHA Cardiovascular Risk Assessment Guidelines. These tailored suggestions may encompass dietary programs, lifestyle modifications, and, when indicated, pharmaceutical therapies like statins, aiming to mitigate identified risks effectively.

Follow-up Procedures

A structured follow-up protocol will be implemented, involving regular contact every six months through phone and email. This proactive approach allows for ongoing participant engagement and the collection of crucial data. Long-term follow-up will extend to tracking ASCVD events, including coronary mortality, myocardial infarction, stroke, and other relevant occurrences, contributing to a comprehensive understanding of disease progression.

Data Analysis and Validation

Demographic and clinical traits will undergo rigorous analysis using descriptive statistics. Subgroup analyses, considering factors such as gender, age, and province, will provide a nuanced perspective on ASCVD risk factors. Statistical tests tailored to data types and study goals will be applied to validate ASCVD risk assessments and ascertain the frequency of events.

Study variables

The study variables encompass a comprehensive set of data points gathered through a dedicated online portal and proforma. Participants will receive unique tracking IDs for recording in an online registry, capturing vital information, including demographic information, clinical history, and outcome measures.

Sample collection and transportation

In terms of sample collection and transportation, a nationwide approach will be adopted, employing standardized protocols for rigorous sample collection, consent procedures, and clinical documentation. All collected samples will be transported to a centralized laboratory, ensuring consistency in processing and analysis. Stringent temperature control, secure logistics, and quality control measures will be implemented to safeguard sample integrity and uphold the highest standards in data reliability and validity.

Outcome Measures

Participants will be stratified into distinct 10-year ASCVD risk categories, including low risk (<5%), borderline risk (5% to <7.5%), intermediate risk (7.5% to <20%), or high risk (≥20%). The 30-year ASCVD risk assessment will utilize the formula proposed by Pencina et al.[23], classifying participants based on their risk for "hard" and "general" CVD events. The lifetime ASCVD risk evaluation will categorize individuals into risk groups, distinguishing between optimal, not optimal, elevated, and major risk factors, determined by specific risk criteria. For Genetic Risk Assessment of ApoB, the study will compute the Genetic Risk Score (GRS) based on genotyping the APOB rs1042031 variant, following the methodology outlined by Shahid SU et al.[24]. The unweighted GRS for ApoB will be derived through an additive approach, assigning values of 0, 1, and 2 for protective homozygous, heterozygous, and risk homozygous genotypes, respectively. This resulting GRS for ApoB will range from 0 (indicating the absence of risk alleles) to 2 (both alleles identified as risk alleles for APOB rs1042031) in an individual.

Data Analysis

The analysis of demographic and clinical characteristics within the research population will be conducted using robust descriptive statistics, providing a comprehensive overview. The distribution of ASCVD risk groups will be meticulously determined to identify prevalent patterns. Subsequently, a thorough subgroup analysis will be undertaken, considering key factors such as gender, age, and province, to unveil nuanced insights into potential variations.

To assess the frequency of ASCVD events and validate the accuracy of risk assessment ratings, a diverse set of statistical tests will be employed, tailored to the data type and study objectives. This includes, but is not limited to, Chi-square tests, ANOVA, or logistic regression analysis, depending on the nature of the variables under consideration. These tests will facilitate a rigorous evaluation of the effectiveness and reliability of our risk assessment models. Additionally, any newly emerging statistical methodologies deemed appropriate for enhancing the precision of our analysis will be thoughtfully incorporated into the study design.

Discussion

The assessment of a patient's risk for atherosclerotic cardiovascular diseases (ASCVD) is crucial in guiding preventive cardiology interventions. This necessitates a holistic approach beyond conventional risk-scoring methods[25]. Primary prevention begins with global risk scoring, using standard office-based factors to calculate ASCVD risk over a specified timeframe, typically 10 years. This risk assessment forms the basis for discussions between clinicians and patients, facilitating the identification of effective cardiovascular disease (CVD) risk reduction strategies. Factors enhancing risk, including premature family history, persistently elevated LDL-C, and chronic kidney disease (CKD), along with inflammatory markers like hsCRP and laboratory measures such as lp(a), play a vital role in informing treatment decisions, enabling a more personalized approach to preventive therapy.

In assessing CVD risk in women, a comprehensive reproductive history is essential, encompassing factors from menarche to menopause, with specific attention to elements like preeclampsia, premature menopause, and autoimmune diseases as risk-enhancing factors. The impact of race/ethnicity on current risk assessment tools must be considered, with certain groups requiring specific attention in preventive therapy decisions. Beyond race/ethnicity, the independent effects of social determinants of health should be integral to clinician-patient discussions when optimizing ASCVD risk. Challenges with the 2013 American College of Cardiology (ACC) and American Heart Association (AHA) Pooled Cohort Equations (PCE) in predicting 10-year risk underscore the need for validation and recalibration based on population-specific factors[26]. Stratification of patients with pre-existing ASCVD according to risk severity is crucial, with very high-risk ASCVD status indicating the necessity for more aggressive treatment, particularly for those with a history of multiple major ASCVD events or recurrent short-term events.

Despite accumulating evidence supporting the superior accuracy of non-HDL cholesterol (HDL-C) and apolipoprotein B (Apo B) in estimating atherosclerotic cardiovascular disease (ASCVD) risk[27-31], current major lipid guidelines persist in recommending LDL cholesterol (LDL-C) as the primary marker to assess treatment adequacy[32,33]. The potential advantages of adopting non-HDL-C or Apo B as treatment targets require further validation, underscoring the ongoing need for continuous efforts to refine ASCVD risk assessment and treatment goals.

A thorough evaluation of ASCVD risk should encompass traditional factors, risk-enhancing elements, reproductive history, social determinants, and advanced screening tests. Integrating these factors into clinician-patient discussions is essential for a personalized and effective approach to ASCVD prevention.

Conflicts of Interest

None.

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