Study Protocol and Statistical Analysis Plan

Title: Progressive Elaboration Framework of Mortality in Treated and Controlled Hypertension: An Observational Study of Pooled Literature and Clinical Data of Contributing Factors to Silent or Uncontrollable Fatal Syndromes

NCT Number: [To be added after PRS registration]

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1. Study Overview

This pooled analysis aims to investigate and synthesize mortality outcomes among individuals with treated and well-controlled hypertension by analyzing available literature and clinical trial data. Despite blood pressure control, a substantial proportion of patients suffer fatal outcomes such as cardiovascular or unexplained death. Understanding the risk factors or underlying mechanisms is essential to guide future research, treatment optimization, and risk stratification.

2. Objectives

To identify and quantify the proportion of deaths in clinical studies among patients with controlled hypertension.

To explore potential contributing factors leading to mortality despite well-controlled BP, including comorbidities, pharmacotherapy, age, and control variability.

To evaluate mortality by subtype: cardiovascular, cerebrovascular, renal, or all-cause.

To generate hypotheses and construct frameworks for future interventional or mechanistic studies.

To explain the end-point without cost, budget or effectiveness associated

3. Study Design

Study Design Type: Observational pooled literature review with meta-analytical approach.

Study Sources: Peer-reviewed articles, published clinical trials (RCTs or open-label), prospective and retrospective cohort studies.

Study type to included:

Interventional studies: RCTs, open-label trials, pragmatic trials.

Non-interventional studies: cohort, case-control, prospective/retrospective observational studies.

Systematic reviews and meta-analyses (if containing extractable arm-level or subgroup-level death data).

Post-hoc or pooled analyses from published trials if mortality is clearly reported in a controlled arm that original study does not report outcomes (Detailed in population)

Inclusion Criteria:

Participants with hypertension under treatment.

Confirmed blood pressure control

Mortality outcome explicitly reported

Includes at least one group/arm/cohort labeled or described as “controlled hypertension” with fatal outcomes recorded.

Population of participants recruit to inclusion criteria for analysis

Human participants of any age group (including neonatal, pediatric, adult, and elderly populations).

Participants with treated and controlled hypertension as defined by the original study authors — not limited to a specific BP threshold (i.e., SBP <140 mmHg or <130 mmHg not required).

Both primary and secondary hypertension types are eligible (e.g., essential, renovascular, endocrine).

All of study include: Explicitly reports death, mortality, or fatal outcome in the context of controlled hypertension, regardless of initial BP value or class of treatment or duration of therapy or

Exclusion Criteria:

Studies not reporting mortality.

Case reports, reviews without primary mortality data.

Animal or in-vitro studies.

Studies focused solely on pulmonary hypertension, glaucoma, or portal hypertension.

Post-hoc, secondary, or sub-analysis reports without baseline data and insufficient raw mortality data.

Cost associated and effectiveness study

Editorials, letters, or opinion papers with no extractable data

4. Statistical Analysis Plan

4.1 Data Extraction

Extracted variables: author, year, study design, number of deaths (per group), mean SBP/DBP, treatment details, follow-up time, comorbidities, event timing, subgroup classification.

Data managed using Zotero, Rayyan, and SRDR+ and COvidence export to STATA

4.2 Outcomes

Primary: All-cause vascular mortality in patients with controlled hypertension meaning Cardiovascular mortality (Cardiac-related death in controlled hypertension patients), cerebrovascular death(Stroke-related fatal outcomes in BP-controlled patients), renal occlusion/rupture/failure causing death (Mortality from renal failure in treated, controlled hypertensives), life-threatening vascular rupture, Major Adverse Cardiovascular Death

Secondary:

Sudden death define death suddenly with autopsy or complete CPR during collapse of cardiac or respiratory or brain arrested

End-organ failure leading to death define vascular abnormality causing failure of organ leading death with evidence by imaging, laboratory investigation or autopsy confirmation

ICU death define systemic arterial hypertension is the main reason for admission at critical care unit report death

Maternal associated hypertension death define from record from healthcare provider confirm pregnancy with or without antenatal care define mortality outcomes of hypertension during pregnancy both from gynecologic organ failure or systemic organ failure

Hypertension associated death in the young define mortality outcomes that clear defined high blood pressure of that age and declared mortality cause during or after any type of treatment

4.3 Analysis Methods

Meta-analysis of proportions and risk ratios (RR) using DerSimonian and Laird random-effects model.

Meta-regression (logistic or Poisson depending on format) for exploring associations (e.g., age, sex, baseline comorbidity, drug class).

Sensitivity analysis excluding high-bias studies or small samples (<100).

Heterogeneity: Assessed using I^2 statistic and Cochrane Q.

Publication bias: Funnel plots and Egger's test.

Software: R (metafor, meta, dmetar), Stata (metan, metareg), Python for transformation.

5. Data Management and Ethics

Public domain published data only; no individual patient data used.

No IRB or informed consent required.

All data will be kept in secure cloud-based repositories (Zotero, Google Drive, GitHub repo for R code)

6. Timeline

Literature screening: July–October 2025

Data extraction: September–December 2025

Analysis: January 2026

Manuscript submission: April 2026

7. Limitations

Variability in BP target definition and control verification.

Incomplete reporting or subgroup data across included studies.

Residual confounding due to observational nature.

8. Expected Outputs

High-quality pooled estimates for mortality outcomes.

Identification of research gaps and clinical predictors.

Protocol transparency for ClinicalTrials.gov posting and PROSPERO (ID: [To be added]) registration.

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