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**CONCEPT SHEET: REGIONAL ANALYSES**

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| **Steering Group approval date:** | *(To be added by UCT data centre)* |
| **Tracking number:** | *(To be added by UCT data centre)* |
| **Title:** | The effect of post-traumatic stress disorder as a causal risk factor for major adverse cardiovascular events: a causal mediation analysis |
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| **Where will statistical analyses be done?** | ISPM, University of Bern |
| **Required variables:** | Sociodemographic data: age, sex, population group, socioeconomic status  Hospital claims, outpatient claims, pharmacy claims, laboratory data, vital status  Administrative data: start and end of medical insurance coverage and health care plan |
| **Target journal:** | Psychological Medicine (DOI: 10.1017/S0033291716002294)  JAMA Cardiology (DOI:10.1001/jamacardio.2021.2530)  Health Psychology (DOI: 10.1037/hea0001127) |
| **Ethics:** | *Select as appropriate:*  This concept uses only the IeDEA-SA standard dataset and is covered by the core IeDEA-SA ethics approvals.  This concept requires additional collection of health-related data, measurements or tests, or sampling of biological material not included in the IeDEA-SA standard dataset. Additional ethics approval is required.\* (Describe ethical considerations for any additional data collection here, including responsible IRBs.) |
| **Milestones:** | *Circulation of concept sheet: June, 2022*  *Ethics approval (for additional data collection): <date>*  *Circulation of mature draft paper: <date>*  *Submission to target journal: <date>* |
| **Abstract:** (about 100 words) | **Background:** Evidence on the association between post-traumatic stress disorders (PTSD) and cardiovascular disease (CVD) is emerging, but there is little empirical support for the causal links between PTSD and CVD.  **Aims:** We aim to examine PTSD as a causal risk factor for major adverse cardiovascular events (MACE) and quantify the mediating effect of PTSD on MACE through CVD risk factors.  **Objectives:**   1. To examine the cumulative incidence and factors associated with PTSD 2. To describe the incidence of CVD risk factors (diabetes, hypertension, dyslipidemia) and MACE in persons with and without PTSD 3. To examine factors associated with CVD risk factors and MACE 4. To examine PTSD as a causal risk factor for MACE (total effect)   **Methods:** We will conduct a retrospective cohort study of South African adults using routine data from a large South African medical insurance scheme. The primary outcome is a three-point MACE (MACE 3), including myocardial infarction, stroke and hospitalization for unstable angina or revascularization procedures. The primary exposure is PTSD. Diabetes, hypertension and dyslipidemia are mediators. The outcome, exposure and mediators will be defined based on clinical results and ICD10 and medical procedure codes from reimbursement claims. We will use Cox regression, parametric g-formula, and survival mediational g-formula to estimate quantities of interest. |

**1. Background**

Post-traumatic stress disorder (PTSD) is a maladaptive reaction to a traumatic event and is present in about 7% of the population (1). The current scientific literature shows an increased incidence of cardiovascular disease (CVD) risk factors (2) and CVD (3) in persons with PTSD.

Two pathways might explain the increased incidence of CVD in persons with PTSD. PTSD can lead to unhealthy behaviours such as substance use, physical inactivity, sleep disorders (4) and dietary changes that lead to CVD risk factors (hypertension, diabetes, high cholesterol), which can cause CVD (2). An alternative explanation is that PTSD causes an effect in several physiological mechanisms that can cause major adverse cardiovascular events (MACE), such as myocardial infarction, unstable angina or stroke. These mechanisms include inflammation, hypothalamic–pituitary–adrenal axis dysregulation and autonomic nervous system imbalances (2). This hypothesis is supported by studies showing that PTSD is independently associated with an increased risk of coronary heart disease even after adjusting for depression and cardiovascular risk factors (3).

The relationship between PTSD and CVD is bidirectional. Evidence suggests that a cardiovascular event can cause PTSD. For example, Edmonson found a 12% prevalence of PTSD secondary to acute coronary syndromes. PTSD, in turn, doubles the risk for recurrent acute coronary syndromes and mortality. The mechanisms through which CVD causally relates to PTSD are under study (2). Moreover, the presence of risk factors, such as obesity, hypertension, diabetes, dyslipidaemia, and inflammation increases the risk of both PTSD and MACE (5).

While evidence on the association between PTSD and CVD is emerging, there is little empirical support for causal links between PTSD and CVD. We aim to examine PTSD as a causal risk factor for MACE and quantify the mediating effect of PTSD on MACE through CVD risk factors.

**2. Objectives**

1. To examine the cumulative incidence and factors associated with PTSD
2. To describe the incidence of CVD risk factors (diabetes, hypertension, dyslipidaemia) and MACE in persons with and without PTSD
3. To examine factors associated with CVD risk factors and MACE
4. To examine PTSD as a causal risk factor for MACE (total effect)

**3. Study design**

We will conduct a cohort study of South African adults using routine data from a large South African medical insurance scheme.

**3.1 Eligibility criteria**

Adults aged 18 years or older with insurance coverage with the medical insurance scheme at any point between January 1, 2011, and March 15, 2020, are eligible for analysis. Persons with unknown sex or age will be excluded.

**3.2 Data sources**

We will use data from a large South African private-sector medical insurance scheme. Data include sociodemographic data, reimbursement claims, laboratory results, information on beneficiaries’ vital status and administrative data on medical insurance coverage.

**3.3 Key variables**

* Sociodemographic data: age, sex, population group, socioeconomic status
* Hospital claims contain the date of admission, date of discharge, International Classification of Diseases, 10th Revision (ICD-10), National Reference Price List (NRPL) codes, and Current Procedural Terminology (CPT) codes.
* Outpatient claims contain ICD-10 diagnoses.
* Pharmacy claims contain information on the active ingredients of drugs coded according to the Anatomical Therapeutic Chemical (ATC) classification system, the drug strengths, the dispensed amount, and the date of dispensing.
* Laboratory data contain the date of specimen collection, the type of laboratory test, the laboratory result, and the unit of measurement.
* Mortality data from the medical scheme records and the National Population Register (NPR): date of death and cause of death (natural/unnatural).
* Administrative data on the start and end of beneficiaries’ medical insurance coverage and the health care plan

**3.4. Assumptions**

The assumptions about the relationship between relevant variables are shown in a directed acyclic graph (DAG) (Figure 1). Population group (ethnicity) and associated socioeconomic disparities affect the risk of PTSD (6) and depressive disorders (7), and lifestyle factors (e.g. smoking, substance use, alcohol use, diet, sleep, and physical activity) (8). Lifestyle factors increase CVD risk factors (e.g. high blood pressure, obesity, high cholesterol, and diabetes) that may cause MACE (9). Population group and socioeconomic disparities are risk factors for HIV (10). HIV is a risk factor for MACE (11). PTSD and depression may lead to lifestyle changes that might lead to CVD risk factors (12). Conversely, after a CVD event, lifestyle might change and so too might CVD risk factors. Depression, PTSD (13), (14)and smoking (15) could also lead to an inflammatory state that increases the risk of MACE. This inflammatory state can also cause PTSD or depression after MACE(16).

**3.5 Measures**

**Outcome:** The primary outcome is a three-point MACE (MACE3), which includes myocardial infarction, stroke, revascularization and hospitalization for unstable angina (Tables 1-2) (17). Secondary outcomes are the two- and four-point MACE (MACE2 and MACE4). MACE2 includes MACE2 includes myocardial infarction and stroke (Tables 1). MACE4 includes MACE3 endpoints and heart failure (Tables 1-2).

**Exposure:** The primary exposure is an ICD-10 diagnosis of PTSD (F43.1).

**Psychiatric comorbidity**

We will consider the following psychiatric comorbidities: substance use disorders (F10-F16, F18-F19), major depressive disorders (F32-F33), psychotic disorders (F20-F29), anxiety disorders (F40-F48, excluding PTSD [F43.1], and sleep disorders (F51, G47).

**Psychiatric medication** will be included through pharmacy claims for antipsychotics (codes xxx)

**Cardiovascular risk factors**

**Hypertension** will be defined based on ICD-10 codes for hypertensive disease (I10-I13, I15, H35.0, and I67.4), evidence of use of medication used to treat hypertension (i.e. certain diuretics, beta-blockers, or drug combinations), or at least two elevated systolic (≥140mmHg), or diastolic (≥90mmHg) blood pressure measurements (Table 3).

**Diabetes mellitus** will be defined based on ICD-10 codes for diabetes (E10-E14, H28, H36, M14.2, M14.6, G59.0, G63.2, or G99.0), evidence of use of medications used for diabetes control (ATC codes A10), or at least two abnormal laboratory results of HbA1c ≥6.5% (≥48 mmol/L), fasting blood glucose ≥7 mmol/L or random blood glucose ≥11.1 mmol/L (Table 4).

**Dyslipidaemia** will be defined based on the ICD-10 codes E78.0-E78.5, evidence of the use of lipid-modifying medication (ATC codes C10), or at least two abnormal lipid measurements (HDL-cholesterol <1 mmol/L, or LDL-cholesterol >4.1 mmol/L, or total cholesterol >6.2 mmol/L) (Table 5).

**Infectious disease**

**HIV** will be defined based on laboratory data for HIV viral load, CD4 count, a positive confirmatory HIV test, an ICD-10 diagnosis for HIV or antiretroviral medication for treating HIV, excluding medication commonly used in pre- or post-exposure prophylaxis (Table 6).

**Sociodemographic characteristics**

We will group age into six categories (18-29, 30-39, 40-49, 50-59, 60-69, and ≥70 years). Population groups will be defined as Black African, Indian/Asian, mixed ancestry [“coloured”], white, or unknown, and sex as male and female.

**Year** will be categorized into three groups: 2011-2013, 2014-2016, 2017-2020

**Statistical methods**

We define baseline as the date of enrolment into the medical insurance scheme, the 18th birthday, or January 1, 2011, whichever occurs later. Persons will be followed from baseline to the end of insurance coverage, death, March 15, 2020, the end of their sixth year of follow-up, or the event of interest, whichever occurs first. PTSD, psychiatric comorbidities, CVD risk factors, HIV, and age will be modelled as time-varying variables. We will split the person-time whenever the value of a time-varying covariate changes. Statistical analysis will be done in R 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) and Stata (Version 16. College Station, TX: StataCorp). If necessary, computations will be done on UBELIX (http://www.id.unibe.ch/hpc), the high-performance computing cluster at the University of Bern, Switzerland.

**Descriptive analysis:** Using descriptive statistics, we will examine baseline characteristics of persons by PTSD status at the end of follow-up.

**Objective 1:** We will estimate the cumulative incidence of PTSD for men, women, and both sexes, taking into account the time-varying nature of the exposure (Simon & Makuch, 1984). We will estimate unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (CIs) for associations between sociodemographic characteristics and PTSD using Cox proportional hazard models.

**Objective 2:** We will estimate the cumulative incidence of diabetes, hypertension, dyslipidaemia, and MACE for persons with and without PTSD, taking into account the time-varying nature of exposure (Simon & Makuch, 1984). We will also estimate the sex-specific cumulative incidence of cardiovascular risk factors and MACE.

**Objective 3:** We will estimate unadjusted and adjusted HR and 95% CIs for factors associated with diabetes, hypertension, dyslipidaemia, and MACE using Cox proportional hazard models. In multivariable analysis, associations between PTSD and outcomes will be adjusted for sociodemographic characteristics, year, HIV, psychiatric comorbidity and medication and CVD risk factors.

**Objectives 4 & 5:** The analyses are based on the structural assumptions summarised in Figure 1. Causal effects are defined as contrasts between counterfactual outcomes. We divide follow-up time into intervals of 6 months. For each interval, we define hypothetical interventions on exposure (PTSD) and mediating factors (CVD risk factors).

**Objective 4:** The total effect of PTSD on the risk of experiencing a MACE by the end of the study period (within six years) is defined as the contrast between the risk of experiencing a MACE if everyone in the population had had PTSD from the beginning to the end of the study and the risk experiencing a MACE if nobody in the population had ever had PTSD. For estimation, standard parametric g-formula will be used. For each time-point we specify parametric models for the distribution of time-varying exposures, mediators, confounders.

**3.7 Ethical considerations**

The Human Research Ethics Committee of the University of Cape Town, South Africa, and the Cantonal Ethics Committee Bern, Switzerland, authorized the analysis of the database. Beneficiaries of the medical insurance scheme provided consent for their data to be used in research.

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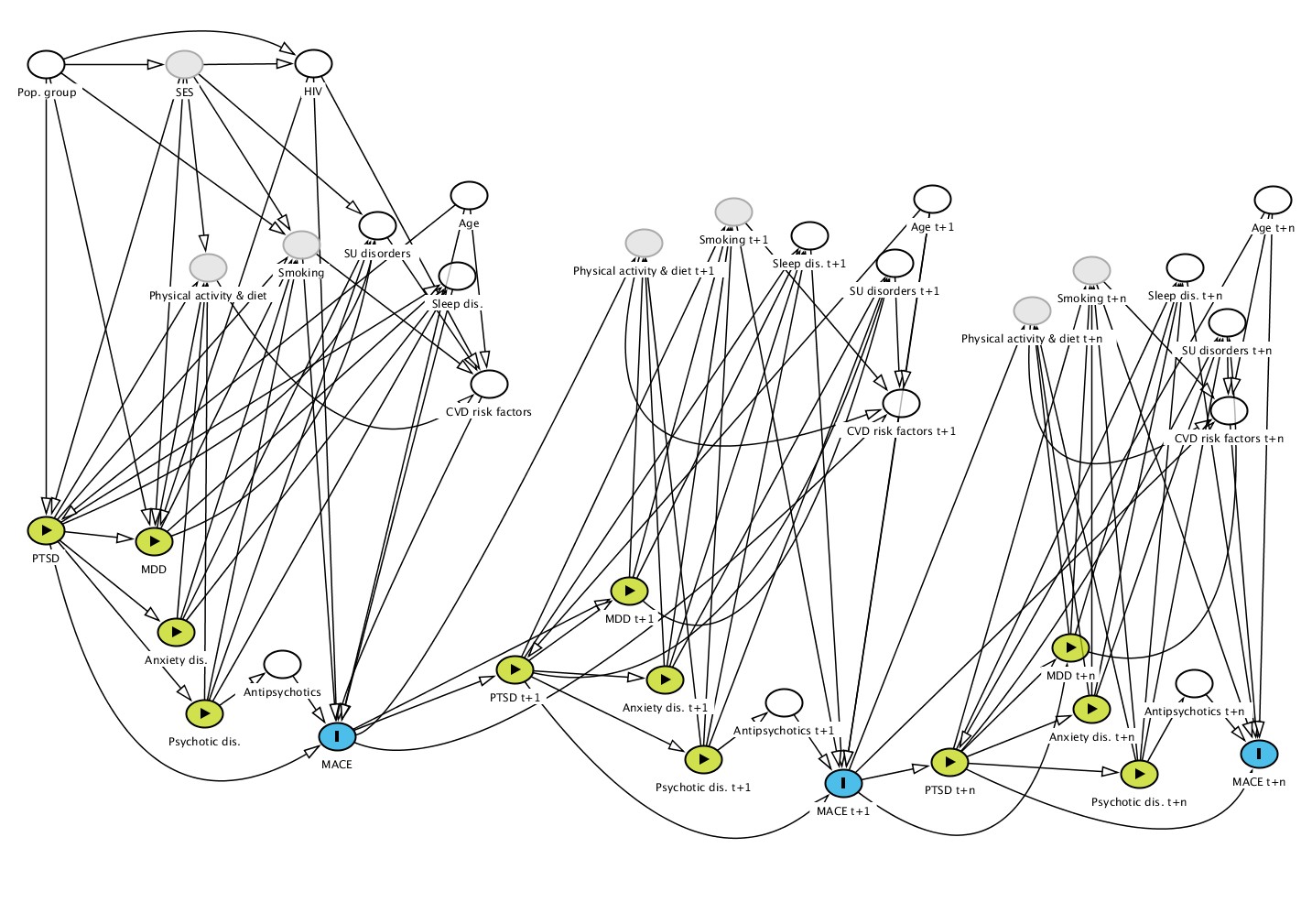
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Figure 1: Directed acyclic graph showing the causal relationship between post-traumatic stress disorder and and major adverse cardiovascular events



SES=socioeconomic status, PTSD=Post-traumatic stress disorder, SU=substance use, MACE=major adverse cardiovascular event, CVD=cardiovascular disease risk factors

Table 1: List of International Classification of Diseases, 10th Revision (ICD-10) codes of acute coronary syndromes, stroke, and heart failure

|  |  |
| --- | --- |
| **Condition** | **ICD-10**  **Code** |
| **Acute coronary syndromes** |  |
| Unstable angina | I20.0 |
| Acute ST-elevation myocardial infarction |  |
| Transmural infarct of anterior wall | I21.0 |
| Transmural infarct of inferior wall | I21.1 |
| Transmural infarct of other sites | I21.2 |
| Transmural infarct of unspecified sites | I21.3 |
| Subsequent (<4w) infarction of anterior wall | I22.0 |
| Subsequent (<4w) infarction of inferior wall | I22.1 |
| Subsequent (<4w) infarction of other sites | I22.8 |
| Subsequent (<4w) infarction of unspecified sites | I22.9 |
| Acute non-ST-elevation myocardial infarction |  |
| Acute subendocardial myocardial infarction | I21.4 |
| Unspecified myocardial infarction |  |
| Acute myocardial infarction, unspecified | I21.9 |
| **Stroke** |  |
| Haemorrhagic stroke |  |
| Subarachnoid haemorrhage from carotid siphon and bifurcation | I60.0 |
| Subarachnoid haemorrhage from middle cerebral artery | I60.1 |
| Subarachnoid haemorrhage from anterior communicating artery | I60.2 |
| Subarachnoid haemorrhage from posterior communicating artery | I60.3 |
| Subarachnoid haemorrhage from basilar artery | I60.4 |
| Subarachnoid haemorrhage from vertebral artery | I60.5 |
| Subarachnoid haemorrhage from other intracranial arteries | I60.6 |
| Subarachnoid haemorrhage from intracranial artery, unspecified | I60.7 |
| Other subarachnoid haemorrhage | I60.8 |
| Subarachnoid haemorrhage, unspecified | I60.9 |
| Intracerebral haemorrhage in hemisphere, subcortical | I61.0 |
| Intracerebral haemorrhage in hemisphere, cortical | I61.1 |
| Intracerebral haemorrhage in hemisphere, unspecified | I61.2 |
| Intracerebral haemorrhage in brain stem | I61.3 |
| Intracerebral haemorrhage in cerebellum | I61.4 |
| Intracerebral haemorrhage, intraventricular | I61.5 |
| Intracerebral haemorrhage, multiple localized | I61.6 |
| Other intracerebral haemorrhage | I61.8 |
| Intracerebral haemorrhage, unspecified | I61.9 |
| Ischaemic stroke |  |
| Cerebral infarction due to thrombosis of precerebral arteries | I63.0 |
| Cerebral infarction due to embolism of precerebral arteries | I63.1 |
| Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries | I63.2 |
| Cerebral infarction due to thrombosis of cerebral arteries | I63.3 |
| Cerebral infarction due to embolism of cerebral arteries | I63.4 |
| Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries | I63.5 |
| Other cerebral infarction | I63.8 |
| Cerebral infarction, unspecified | I63.9 |
| Central retinal artery occlusion | H34.1 |
| Unspecified stroke |  |
| Stroke, not specified as haemorrhage or infarction | I64 |
| **Heart failure** |  |
| Heart failure due to hypertension | I11.0 |
| Congestive heart failure | I50.0 |
| Left ventricular failure, unspecified | I50.1 |
| Systolic (congestive) heart failure | I50.2 |
| Diastolic (congestive) heart failure | I50.3 |
| Combined systolic (congestive) and diastolic (congestive) heart failure | I50.4 |
| Other heart failure | I50.8 |
| Heart failure, unspecified | I50.9 |
| Other postprocedural cardiac functional disturbances | I97.1 |

Table 2: List of Current Procedural Terminology (CPT) codes for coronary revascularisation procedures

|  |  |
| --- | --- |
| **Procedure** | **CPT code** |
| Coronary revascularisation procedures |  |
| Coronary artery graft | 33503 |
| Coronary artery graft | 33504 |
| Coronary artery bypass graft, vein, single | 33510 |
| Coronary artery bypass graft, vein, two | 33511 |
| Coronary artery bypass graft, vein, three | 33512 |
| Coronary artery bypass graft, vein, four | 33513 |
| Coronary artery bypass graft, vein, five | 33514 |
| Coronary artery bypass graft, vein, six or more | 33516 |
| Coronary artery bypass graft, artery-vein, single | 33517 |
| Coronary artery bypass graft, artery-vein, two | 33518 |
| Coronary artery bypass graft, artery-vein, three | 33519 |
| Coronary artery bypass graft, artery-vein, four | 33521 |
| Coronary artery bypass graft, artery-vein, five | 33522 |
| Coronary artery bypass graft, artery-vein, six or more | 33523 |
| Coronary artery, bypass/reoperation | 33530 |
| Coronary artery bypass graft, arterial, single | 33533 |
| Coronary artery bypass graft, arterial, two | 33534 |
| Coronary artery bypass graft, arterial, three | 33535 |
| Coronary artery bypass graft, arterial, four or more | 33536 |
| Open coronary endarterectomy | 33572 |
| Percutaneous transluminal coronary angioplasty, single major coronary artery or branch | 92920 |
| Percutaneous transluminal coronary angioplasty, each additional branch of major coronary artery | 92921 |
| Percutaneous transluminal coronary atherectomy, with coronary angioplasty when performed; single major coronary artery or branch | 92924 |
| Percutaneous transcatheter placement of intracoronary stent(s), with coronary angioplasty when performed; single major coronary artery or branch | 92928 |
| Percutaneous transcatheter placement of intracoronary stent(s), with coronary angioplasty when performed; each additional branch of a major coronary artery | 92929 |
| Percutaneous transluminal coronary atherectomy, with intracoronary stent, with coronary angioplasty when performed; single major coronary artery or branch | 92933 |
| Percutaneous transluminal coronary atherectomy, with intracoronary stent, with coronary angioplasty when performed; each additional branch of a major coronary artery | 92934 |
| Percutaneous transluminal revascularisation of or through coronary artery bypass graft (internal mammary, free arterial, venous), any combination of intracoronary stent, atherectomy and angioplasty, including distal protection when performed; single vessel | 92937 |
| Percutaneous transluminal revascularisation of or through coronary artery bypass graft (internal mammary, free arterial, venous), any combination of intracoronary stent, atherectomy and angioplasty, including distal protection when performed; each additional branch subtended by the bypass graft | 92938 |
| Percutaneous transluminal revascularisation of acute total/subtotal occlusion during acute myocardial infarction, coronary artery or coronary artery bypass graft, any combination of intracoronary stent, atherectomy and angioplasty, including aspiration thrombectomy when performed, single vessel | 92941 |
| Percutaneous transluminal revascularisation of chronic total occlusion, coronary artery, coronary artery branch, or coronary artery bypass graft, any combination of intracoronary stent, atherectomy and angioplasty; single vessel | 92943 |
| Percutaneous transluminal revascularisation of chronic total occlusion, coronary artery, coronary artery branch, or coronary artery bypass graft, any combination of intracoronary stent, atherectomy and angioplasty; each additional coronary artery, coronary artery branch, or bypass graft | 92944 |
| Percutaneous transluminal coronary thrombectomy | 92973 |
| Insert intracoronary stent | 92980 |
| Insert intracoronary stent | 92981 |
| Coronary artery dilation | 92982 |
| Coronary artery dilation | 92984 |

Table 3: List of diagnoses, medications, and test results indicative of hypertension

|  |  |
| --- | --- |
| **Diagnoses** | **ICD10 code** |
| Essential hypertension | I10 |
| Hypertensive heart disease | I11 |
| Hypertensive renal disease | I12 |
| Hypertensive heart and renal disease | I13 |
| Secondary hypertension | I15 |
| Hypertensive retinopathy | H35.0 |
| Hypertensive encephalopathy | I67.4 |
| **Drug** | **ATC code** |
| Low-ceiling diuretics (thiazides) | C03A |
| Low-ceiling diuretics (non-thiazides) | C03B |
| Low-ceiling diuretics in combination with potassium-sparing agents | C03EA |
| Beta-blockers combined with thiazides | C07B |
| Beta-blockers with “other” diuretics | C07C |
| Beta-blockers with thiazide diuretic with "other" diuretics | C07D |
| Calcium channel blockers in combination with diuretics | C08G |
| ACE-inhibitors with diuretics | C09BA |
| Angiotensin II receptor-blockers with diuretics | C09DA |
| Valsartan + amlodipine + hydrochlorothiazide | C09DX01 |
| Olmesartan + amlodipine + hydrochlorothiazide | C09DX03 |
| Candesartan + amlodipine + hydrochlorothiazide | C09DX06 |
| Aliskiren + hydrochlorothiazide | C09XA52 |
| Aliskiren + amlodipine + hydrochlorothiazide | C09XA54 |
| Rosuvastatin + perindopril + indapamide | C10BX13 |
| **Clinical test** | **Value** |
| Systolic blood pressure | ≥140mmHg |
| Diastolic blood pressure | ≥90mmHg |

Table 4: List of diagnoses, medications, and laboratory test results indicative of diabetes mellitus

|  |  |
| --- | --- |
| **Diagnoses** | **ICD10 code** |
| Type 1 diabetes mellitus | E10 |
| Type 2 diabetes mellitus | E11 |
| Malnutrition-related diabetes mellitus | E12 |
| Other specified diabetes mellitus | E13 |
| Unspecified diabetes mellitus | E14 |
| Diabetic cataract | H28.0 |
| Diabetic retinopathy | H36.0 |
| Diabetic arthropathy | M14.2 |
| Diabetic neuropathic arthropathy | M14.6 |
| Diabetic mononeuropathy | G59.0 |
| Diabetic polyneuropathy | G63.2 |
| Diabetic autonomic neuropathy | G99.0 |
| **Drug** | **ATC code** |
| Drugs used in diabetes | A10 |
| **Laboratory test** | **Value** |
| HbA1c | ≥6.5 % (≥48mmol/L) |
| Fasting blood glucose | ≥7.0 mmol/L (~126 mg/dL) |
| Random blood glucose | ≥11.1 mmol/L (~200 mg/dL) |

Table 5: List of diagnoses, medications, and test results indicative of dyslipidaemia

|  |  |
| --- | --- |
| **Diagnoses** | **ICD10 code** |
| Pure hypercholesterolaemia | E78.0 |
| Pure hyperglyceridaemia | E78.1 |
| Mixed hyperlipidaemia | E78.2 |
| Hyperchylomicronaemia | E78.3 |
| Other hyperlipidaemia | E78.4 |
| Hyperlipidaemia, unspecified | E78.5 |
| **Drug** | **ATC code** |
| Lipid-modifying agents | C10 |
| **Laboratory test** | **Value** |
| HDL-cholesterol | <1 mmol/L (~40 mg/dL) |
| LDL-cholesterol | >4.1 mmol/L (~160 mg/dL) |
| Total cholesterol | >6.2 mmol/L (~240 mg/dL) |

Table 6: List of diagnoses, medications, and test results indicative of HIV

|  |  |
| --- | --- |
| **Diagnoses** | **ICD10 code** |
| Human immunodeficiency virus (HIV) disease | B20-B24 |
| Asymptomatic HIV infection status | Z21 |
| Laboratory evidence of HIV | R75 |
| HIV disease complicating pregnancy, childbirth and the puerperium | O98.7 |
| **Antiretroviral medication for treating HIV** | **ATC code** |
| Protease inhibitors | J05AE |
| Nucleoside and nucleotide reverse transcriptase inhibitors | J05AF |
| Non-nucleoside reverse transcriptase inhibitors | J05AG |
| Integrase inhibitors | J05AJ |
| Antivirals for treatment of HIV infections, combinations | J05AR |
| **Antiretroviral medication used in pre- or post-exposure prophylaxis** | **ATC code** |
| Tenofovir disoproxil and emtricitabine (TDF/FTC) | J05AR03 |
| Tenofovir alafenamide (TAF) | J05AF13 |
| Emtricitabine (FTC) | J05AF09 |
| Lamivudine (3TC) | J05AF05 |
| **Laboratory test** | **Value** |
| Confirmatory HIV test | Positive |