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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:** |  |
| **Lead author:**  **Email:** | Cristina Mesa Vieira (ISPM)  Cristina.mesavieira@ispm.unibe.ch |
| **IeDEA senior investigator:**  **Email:** | Andreas Haas (ISPM)  [andeas.haas@ispm.unibe.ch](mailto:andeas.haas@ispm.unibe.ch) |
| **Statisticians:**  **Email:** | Christiane Didden, Cristina Mesa Vieira, Andreas Haas  Christiane.didden@ispm.unibe.ch |
| **Data manager:**  **Email:** | Andreas Haas (ISPM) |
| **Where will statistical analyses be done?** | ISPM, University of Bern |
| **Required variables:** | Sociodemographic data: age, sex, ethnicity, 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: April 1, 2022*  *Ethics approval (for additional data collection): <date>*  *Circulation of mature draft paper: <date>*  *Submission to target journal: <date>* |
| **Abstract:** (about 100 words) | **Background:**  **Aims and objectives:**  **Methods:** |

**1. Background**

Posttraumatic stress disorder (PTSD) is a maladaptive reaction to a traumatic event, and it is present in about 7% of the population (1). The current scientific literature shows an association between PTSD and CVD risk factors (2) and cardiovascular disease (CVD). For example, a recent systematic review (3) reported that persons with PTSD had a largely increased risk of subsequent myocardial infection (HR 1.49, 95% CI 1.31-1.69).

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 and dietary changes that lead to common cardiovascular risk factors (hypertension, diabetes, high cholesterol), which can cause CVD (2). An alternative explanation is that PTSD generates an inflammatory state that can cause CVDs such as myocardial infarction, unstable angina and stroke (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, such as high cholesterol, hypertension and high blood pressure (3). Sleep disorders are common in patients with PTSD and have been also described as a risk factor for CVD (4).

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).

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 CVD and quantify the mediating effect of PTSD on CVD through CVD risk factors.

**2. Objectives**

1. To describe the incidence of CVD risk factors (diabetes, hypertension, dyslipidaemia) and major adverse cardiovascular events (MACE) in persons with and without PTSD
2. To examine PTSD as a causal risk factor for MACE (total effect)
3. To quantify the mediating effect of PTSD through CVD risk factor on MACE (indirect effect via mediators).

**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 who had 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, ethnicity
* 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). Ethnicity and associated socioeconomic disparities affect the risk of PTSD (5) and depression (6), and lifestyle factors (e.g. smoking, substance use, alcohol use, diet, sleep, and physical activity) (7). Lifestyle factors increase CVD risk factors (e.g. high blood pressure, obesity, high cholesterol, and diabetes) that may cause MACE (8). Ethnicity and socioeconomic disparities are risk factors for HIV (9). HIV is a risk factor for MACE (10). PTSD and depression may lead to lifestyle changes that might lead to CVD risk factors (11). Conversely, after a CVD event, lifestyle might change and thus the CVD risk factors. Depression, PTSD (12), and smoking (13) could also lead to an inflammatory state that increases the risk of MACE. This inflammatory state can also cause PTSD or depression after MVE (14).

**3.5 Measures**

**Outcome:** The primary outcome is a two-point major adverse cardiovascular event (2-P MACE) which includes as an acute myocardial infarction or stroke. Cases of acute myocardial infarction are defined in the presence of any of the ICD-10 codes for acute ST-elevation myocardial infarction, acute non-ST-elevation myocardial infarction, or unspecified myocardial infarction. Cases of stroke are defined in the presence of hemorrhagic, ischaemic ir unspecified stroke (Table 1). We will also use a three-point MACE (3-P MACE), that includes the ICD-10 codes of the 2-P MACE plus hospitalization for angina or hospitalization procesdures (Table 2). Finally, a four-point MACE includes the codes in the 3-P MACE in addition to the ICD-10 codes for heart failure (Table 3).

**Exposure:** The primary exposure is an ICD-10 diagnosis of PTSD (F43.1). The secondary exposures include ICD-10 diagnoses of organic mental disorders (F00-F09), substance use disorders (F10-F16, F18-F19), psychotic disorders (F20-F29, R44.0-R44.3), mood disorders (F30-F39), other anxiety disorders (F40-F48, excluding PTSD [F43.1], and unspecified anxiety disorders [F41.9]) sleep disorders (F51, G47) or other mental disorders (F50, F52-F99). Exposure variables will be defined as time-varying variables. Persons will be considered “exposed” from the date of their first diagnosis onwards.

**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 4).

**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 5).

**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 6).

**Infectious disease**

**HIV** will be defined based on laboratory data for HIV viral load, CD4 count, or a positive confirmatory HIV test, an ICD-10 diagnosis for HIV or the use of antiretroviral medication for treating HIV excluding medication commonly used in pre- or post-exposure prophylaxis (Table 7).

**Overweight and obesity** will be defined based on ICD-10 codes (E66).

**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.

* 1. **Statistical methods**

**Objective i:**Expousre variables, defined as a time-varying binary variable. Patients will be considered unaffected by PTSD (unexposed) until they had received the first diagnosis. Thereafter, they are considered to be exposed. We use descriptive statistics to analyze characteristics of participants with and without PTSD.

We consider the diagnosis of a major adverse cardiovascular event (MACE) and the diagnosis of a cardiovascular risk factor – hypertension, diabetes, overweight - as distinct events. For each, we perform the following analyses: We estimate the cumulative incidence of the outcome, taking into account the time-varying nature of exposure (Simon & Makuch, 1984).

We estimate unadjusted and adjusted Hazard Ratios (HR) and 95% Confidence Intervals (CIs) using Cox proportional hazard models. In multivariable Cox regression, we adjust for sociodemographic characteristics including age, sex, ethnicity, SES as well as HIV and tuberculosis as time-varying covariates. With respect to MACE, cardiovascular risk factors will be included in the adjustment set of another Cox model to assess whether there remains an association between PTSD and MACE after controlling for cardiovascular risk factors.

*Objective ii & iii:* The analyses are based on the structural assumptions summarized in Figure 1. Causal effects are defined as contrasts between counterfactual outcomes. We divide time into intervals of 6 months. For each interval, we define hypothetical interventions on exposure (PTSD) and mediating cardiovascular risk factors (hypertension, diabetes, overweight).

*Objective ii:* The total effect of PTSD on the risk of being diagnosed with CVD by the end of the study period (within eight years (2012-2020) is defined as the contrast between the risk of being diagnosed with CVD if everyone in the population had had PTSD from the beginning to the end of the study and the risk of being diagnosed with CVD if everyone in the population had never had PTSD. For estimation, standard parametric g-formula is used. For each time-point we specify parametric models for the distribution of time-varying exposures, mediators, confounders.

*Objective iii:* For the effects of PTSD on CVD mediated by cardiovascular risk factors, interventional indirect effects are defined. The following indirect effects are of interest: 1) The interventional indirect effect through the cardiovascular risk factors considered jointly, 2) the interventional indirect effects via each of the cardiovascular risk factors considered separately. For estimation, the survival mediational g-formula is applied (Lin, Young, Logan, & VanderWeele, 2017; Lin, Young, Logan, Tchetgen Tchetgen, et al., 2017).

Main challenges of the causal analyses are correct model specification as well as unmeasured confounding. Unmeasured variables are, for example, time-varying lifestyle characteristics such as diet, physical activity, sleep, as well as substance use (see Figure 1). We assume that these unmeasured factors affect the CVD outcome via measured cardiovascular risk factors. That is, by adjusting appropriately for cardiovascular risk factors, confounding induced by unmeasured lifestyle factors is attenuated.

**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 or their guardians provided consent for their data to be used in research.

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Figure 1: Directed acyclic graph (DAG) showing the assumptions about the relationship between variables influencing the relationship between posttraumatic stress disorder and major cardiovascular eventsFigure 1: Directed acyclic graph showing the causal relationship between posttraumatic stress disorder and cardiovascular diseases

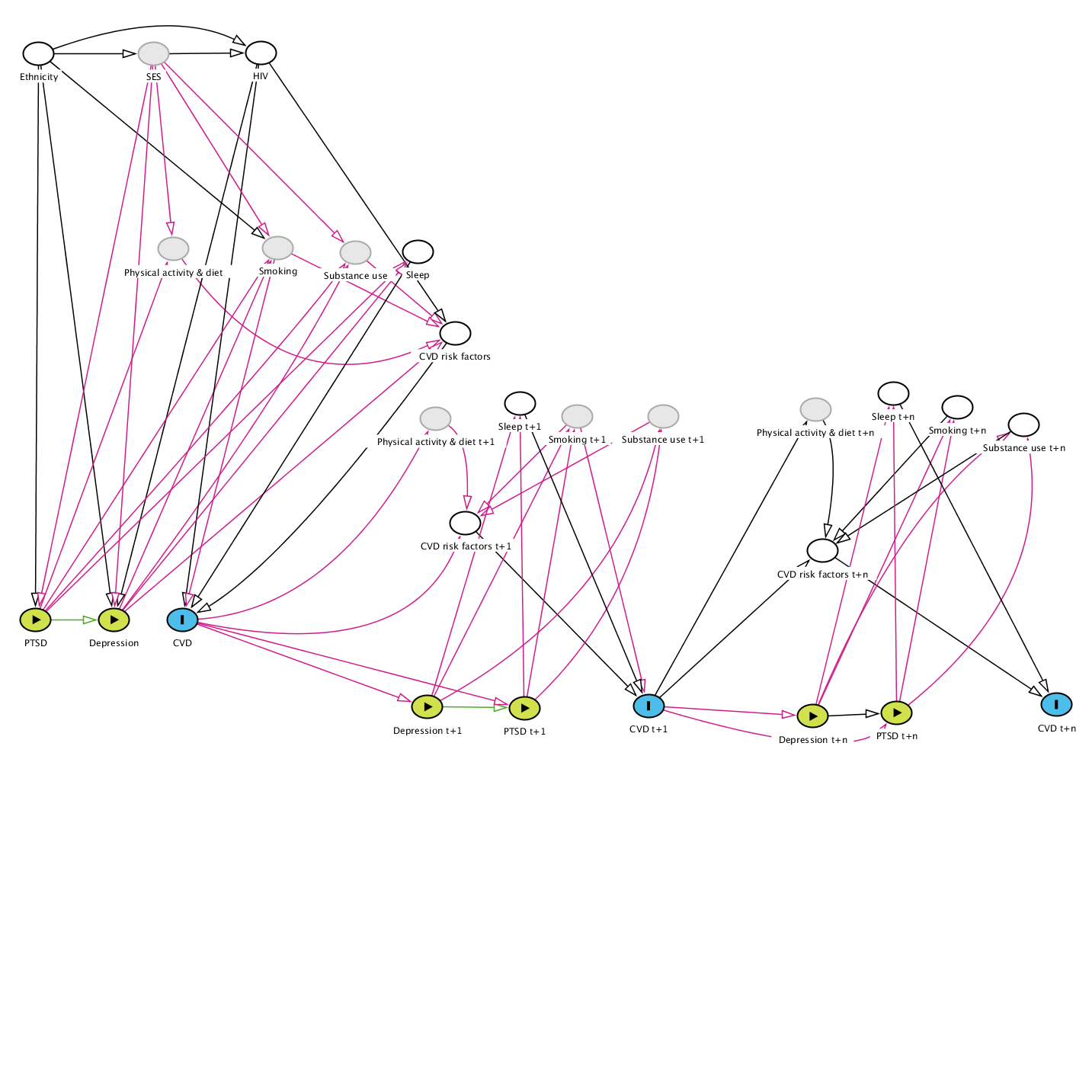


Table 1: Two-point MACE. List of International Classification of Diseases, 10th Revision (ICD-10) codes of acute coronary syndromes and stroke

|  |
| --- |
| **ConditionICD-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 |

Table 2: Three-point MACE. List of Current Procedural Terminology (CPT) codes for coronary revascularization procedures indicative of major cardiovascular events

|  |  |
| --- | --- |
| **Procedure** | **CPT code** |
| Coronary revascularization 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 revascularization 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 revascularization 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 revascularization 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 revascularization 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 revascularization 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: Four-point MACE list of International Classification of Diseases, 10th Revision (ICD-10) codes of acute coronary syndromes and stroke

|  |  |
| --- | --- |
| **Condition** | **ICD-10**  **Code** |
| Heart failure |  |
| Heart failure due to hypertension  Heart failure | I11.0 |
| 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 4: 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 5: 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 6: 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 7: 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 |