consortium for SPINAL CORD MEDICINE
CLINICAL PRACTICE GUIDELINES

CLINICAL PRACTICE GUIDELINES: SPINAL CORD MEDICINE

Identification and Management of Cardiometabolic Risk after Spinal Cord Injury

Clinical Practice Guideline for Health Care Providers

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Administrative and financial support provided by Paralyzed Veterans of America

These guidelines have been prepared based on scientific and professional information available in 2018. Users should periodically review this material to ensure that the advice herein is consistent with current reasonable clinical practice. The websites noted in this document were current at the time of publication; however, because web addresses and the information contained therein change frequently, the reader is encouraged to stay apprised of the most current information.

Preface

Cardiometabolic disease (CMD) can be thought of as a silent killer. The clinical manifestations of this secondary complication of spinal cord injury (SCI) may not be apparent until too late to intervene. Until now, CMD has been less of a focus of the SCI community as a whole, compared to the other major secondary conditions of neurogenic bowel and bladder, autonomic dysfunction, respiratory insufficiency, depression, sexual dysfunction, pressure injuries, and venous thromboembolism, which are overt in their presentation and have been addressed in previous guidelines.

The recommendations of this Clinical Practice Guideline (CPG) regarding identifying and managing CMD risks are in line with current recommendations for identifying and managing CMD risks in people without SCI, which have also been recently updated. However, these recommendations also take into consideration the differences between the body composition and physiology of those with SCI and those without SCI, and the risks of certain interventions for persons with SCI, given the presence of other secondary conditions such as neurogenic bowel, and also acknowledge the challenges to implementating the recommendations within the SCI community.

We were fortunate in the development and peer review of this CPG to have representation from all the various stakeholders and subspecialties impacted by these recommendations, including a range of experts in nutrition, exercise, cardiology, endocrinology, internal medicine and rehabilitation. This wide-ranging representation will hopefully translate into uniform, quality practice through the widespread use of this CPG to guide CMD prevention and treatment in all settings, which can only result in the best outcomes and least amount of morbidity and mortality for those who experience SCI.

On behalf of the consortium steering committee, I want first to acknowledge the leadership of the guideline panel, namely the Chair, Mark Nash, and Co-Chair Suzanne Groah, in guiding this panel through the ups and downs of a development process which spanned five years. The panel members themselves, who kept to task for so long, and the many reviewers who provided valuable feedback from all areas, are to be commended. Everyone, including the panel Chair and Co-Chair, volunteered their time to help produce this superb document. In addition, I wish to acknowledge the ongoing support of Paralyzed Veterans of America (Paralyzed Veterans), especially President David Zurfluh, Executive Director Carl Blake, and Director of Research and Education Cheryl Vines, as well as the rest of the leadership team, without whose support these guidelines would not exist.

Thomas N. Bryce, MD
Chair, Steering Committee
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Foreword

The following Guideline is the first from the Consortium for Spinal Cord Medicine to address CMD after SCI. In doing so, it reports the emergence of all-cause cardiovascular diseases (CVD) and CVD-related risks as significant health hazards for persons with SCI and establishes a foundational standard for identification and management of cardiometabolic risks. The spinal cord community was first made aware of these risks in the early 1980s. Since then, hundreds of scholarly articles have examined antecedents, causes, personal and population characteristics, co-morbidities and treatments for these hazards. These studies have confirmed that persons with SCI are frequently sedentary, overweight, dyslipidemic and at elevated risk for insulin resistance, thus placing them in jeopardy of developing CMD. None of the health hazards imposed by the five archetypical CMD risk components foretells the long, active, productive, and healthy life we seek for persons with SCI. These conditions may also prohibit persons with SCI from undergoing, or ultimately benefiting from, the restorative therapies in clinical trials, or from using rehabilitation technologies that require a relatively lean and healthy body for their efficient use.

Unlike some diseases and disorders addressed by other Consortium Guidelines, CMD typically develops slowly and without overt symptoms. Unless routinely surveilled in the SCI population, CMD may be irreversible once clinically detected. The panel seriously considered the possibility that CMD and its component risks, once identified, will be far more challenging to treat in persons with SCI than their non-disabled counterparts. For these reasons, this guideline will favor scheduled surveillance, early risk assessment, timely symptom recognition, and prudent interventional care. In arriving at these recommendations, the Panel asserts that an enlightened and compassionate health care system, and a caring society, will unquestionably favor early assessment and aggressive preemptive care when not doing so might result in early morbidity and uncertain mortality.

The consumers of this guideline – health professionals and stakeholders with SCI– will note that its evidence and opinions may sometimes point to persons with SCI being at no greater risk for a diagnosis of CMD or its component risks than their non-disabled cohorts. It should be emphasized, however, that all-cause CVD and related conditions are among the most prevalent, life threatening, function compromising and costly of known medical hazards. In making recommendations, the Panel has also taken into consideration that our health care system is even less prepared to effectively treat CMD in those with SCI than to prevent it. Given these circumstances, we believe it is practical to embrace primary prevention as a best-practice, strategic approach. In some instances, the Panel found no evidence or clinical intuition to sidestep the adoption of several recommendations that currently exist for CMD diagnosis and management in the general population. These strategic guidelines provide an extensively vetted, evidence-based standard in cases where no such guideposts have been fashioned or applied for the benefit of the SCI population. When adopting standards used for the general population, we have also identified areas in need of investigation so that the foundational evidence for CMD identification and management can become even more representative of, and relevant for, the SCI population.

In publishing the Guideline, we extend our sincerest thanks for the dedicated work and meaningful contributions of Panel Members, Drs. Trevor Dyson-Hudson, David Gater, Jesse Lieberman, Jonathon Myers, Sunil Sabharwal and Allen Taylor. We further note with appreciation the contributions of Ms. Cheryl Vines, Dr. Thomas Bryce, the Paralyzed Veterans CPG Steering Committee, and the Consortium Partners who collectively recognized the importance of this topic and unfailingly supported the Panel's activities to their completion.

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Acknowledgements

Paralyzed Veterans is proud to sponsor the development and dissemination of the SCI CPGs. For over twenty years we have partnered with the Consortium of Spinal Cord Medicine in a shared mission to improve the health of individuals living with SCI. Today, hundreds of thousands of copies of the guidelines are used around the world by physicians and other medical professionals who provide care to individuals living with SCI at every level, from the emergency department to acute care, rehabilitation to community services.

We thank Dr. Nash and Dr. Groah for their leadership and perseverance in guiding this important new guideline into practice. Sincere thanks is also extended to all panel members who worked tirelessly, without remuneration, to bring this project to fruition.

As with any project of this magnitude, many were involved in the process. Sincere appreciation goes to Dr. Shelly Selph and her team at the Pacific Northwest Evidence-based Practice Center, Oregon Health and Science University, who conducted the review of literature and methodology for this guideline.

We would like to acknowledge attorney William H. Archambault for conducting a comprehensive analysis of the legal and health-policy issues associated with this complex, multifaceted topic.

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Finally, it is only with the significant, mission-driven support of Paralyzed Veterans, our leadership and our members, that we are able to provide these services. Sincere thanks to Paralyzed Veterans President David Zurfluh, Past President Al Kovach and Executive Director Carl Blake for their support.

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Glossary

2-Compartment Modeling for Body Composition: a technique used for body-composition analysis that discriminates body fat mass from the fat-free mass.

3-Compartment Modeling for Body Composition: a technique used for body-composition analysis that discriminates fat mass, total body water and fat-free mass.

4-Compartment Modeling for Body Composition: a technique used for body-composition analysis that discriminates fat mass, total body water, bone mineral mass and fat-free mass.

ACC: American College of Cardiology

ACSM: American College of Sports Medicine

ADA: American Diabetes Association

AHA: American Heart Association

Anorexigenic: any drug, herbal or nutraceutical agent that promotes a loss of appetite.

Apolipoprotein-A1 (Apo-A1): the major protein component of HDL particles in plasma that clears cholesterol from within artery walls; its presence is associated with reduced cardiovascular disease risk.

Apolipoprotein B (Apo B): the primary Apolipoprotein of chylomicrons, VLDL, IDL, and LDL particles that transports lipids, including cholesterol, to body tissues. High levels of ApoB, especially associated with the higher LDL particle concentrations, are the primary instigators of vascular plaques leading to heart disease and stroke.

ASCVD: atherosclerotic cardiovascular disease

Autonomic: referring to involuntary or unconscious activities regulated by the sympathetic or parasympathetic branches of the autonomic nervous system.

Bariatric Procedures: minimally invasive and invasive (open) surgical procedures that foster weight loss by any one or any combination of the following mechanisms: 1. restricting the amount of food the stomach can hold 2. causing malabsorption of nutrients or 3. both. Bariatric procedures also often cause hormonal changes. The most common bariatric surgery procedures are gastric bypass, sleeve gastrectomy, adjustable gastric band and biliopancreatic diversion with duodenal switch. Each surgery has advantages and disadvantages.

Beta-blocker: a class of pharmaceutical agents used primarily for the treatment of hypertension, myocardial infarction and congestive heart failure. Beta-blockers selectively or non-selectively block beta-adrenergic receptors, thus lowering blood pressure via lowered heart rate and stroke volume, a vasodilator effect, and diuresis.

BF: body fat

Body Mass Index (BMI): a proxy for determination of overweight and obesity, calculated as the body mass (kg) divided by the square of body length or height (m). In persons with SCI, evidence supports a BMI ≥ 22 kg/m2 as representing an obese body habitus.

BP: blood pressure

Cardiometabolic Disease (CMD): A clustering of interrelated risk factors that promote the development of atherosclerotic vascular disease and Type 2 diabetes mellitus. The disease is comprised of maladaptive cardiovascular, renal, metabolic, pro-thrombotic and inflammatory pathologies, and has five component risks: obesity, insulin resistance, hypertension and dyslipidemia (as low HDL and elevated TG).

Cardiovascular Disease (CVD): conditions that involve narrowed or blocked blood vessels that result in myocardial ischemia and infarction, angina or stroke.

CMD Risk Components: health hazards that comprise the risk determination for CMD. According to the AHA guidelines, they include obesity, insulin resistance, hypertension and dyslipidemia, the latter as low HDL-C and elevated TG.

C - reactive protein (CRP): an acute-phase reactant and clinical biomarker that signposts non-specific inflammation

DASH Diet: "Dietary Approaches to Stop Hypertension" nutritional plan, which is primarily intended for hypertension management, but can also be used as a body mass reduction strategy. The plan promotes more fruits, vegetables and low-fat dairy foods; limits foods that are high in saturated fat, cholesterol, and trans fats; encourages whole-grain foods, fish, poultry, and nuts; and restricts sodium, high glycemic (i.e., faster metabolized or simple) sugars, sugar-laden drinks and red meats.

Diabetes (Db)/Pre-Diabetes: a disease in which the body's ability to produce or respond to the hormone insulin is impaired, resulting in the dysfunctional metabolism of carbohydrates and elevated levels of glucose in blood and urine. Pre-diabetes is characterized by slightly elevated blood glucose levels and is regarded as a high-probability risk for ultimately progressing to Type-2 diabetes. Unlike the Type-1 Db form, in which the beta-cells of the pancreas are destroyed by an autoimmune reaction, Type-2 Db is considered the result of insulin resistance and is associated with obesity, dysglycemia, dyslipidemia and vascular inflammation.

Diastolic blood pressure (DBP): the minimum arterial pressure during the cardiac filling phase.

Dyslipidemia: a general term used to describe abnormal levels of blood triglycerides, cholesterol and lipoprotein cholesterols suggestive of elevated risk for all-cause CVD. When used to describe CMD-related risk, the term specifically describes low levels of high-density lipoprotein cholesterol and elevated triglycerides.

Fasting Plasma Glucose (FPG): A diagnostic test that measures glucose in blood plasma following a fast lasting at least 8 hours. Fasting plasma levels are defined as normal, pre-diabetes, or diabetes based upon criterion scores.

Fasting Blood Glucose (FBG): a clinical test to determine the amount of glucose in the blood. Primarily used in screening for prediabetes or diabetes, FBG is tested following eight hours without food intake.

Fat-Free Mass (FFM): also known as lean body mass and primarily referencing muscle mass, it includes body water, bone, organs and muscle masses.

GI: gastrointestinal

Glucose Intolerance (also Impaired Glucose Tolerance) (IGT): an intermediate, pre-diabetic state of glucose dysregulation associated with insulin resistance and increased risk of cardiovascular pathology. This pathology has a high probability of advancing to Type-2 Diabetes Mellitus and represents a component risk for CMD and mortality. IGT is defined by an elevated 2-h plasma glucose concentration (≥140 and <200 mg/dl) after a 75-g glucose load on the oral glucose tolerance test (OGTT) in the presence of an FPG concentration <126 mg/dl.

Glycated Hemoglobin (HbA1c or A1C): a clinical test that serves as a proxy for average blood glucose over a three-month period. Levels above 7% reflect poor control of blood glucose and elevated risk for microangiopathy and CVD.

High-Density Lipoprotein (HDL) Cholesterol: a lipoprotein contained in blood plasma composed of a high proportion of protein with limited triglycerides and cholesterol. High levels are associated with reduced risk of atherosclerosis and, when above certain levels, are considered cardioprotective. Cut-scores for elevated risk are HDL-C < 40 mg/dl in males and < 50 mg/dL in females.

hs-CRP: reference to the laboratory technique used for measuring low levels of CRP with "high sensitivity."

Indirect Calorimetry (IC): a clinical technique that measures inspired and expired gas flow, volumes and concentrations of O2 and CO2, and permits measurement of oxygen consumption and carbon dioxide production. These values can be used to express caloric expenditure and work intensity.

Inflammatory Cytokines: immunomodulating signaling molecules (chemokines, interferons, interleukins, and lymphokines) excreted from immune and other cells that promote inflammation.

Homeostatic Model Assessment for Insulin Resistance (HOMA)-IR: A proxy method for determining insulin resistance from fasting glucose and insulin or C-peptide concentrations.

Hypertension: chronic elevation of blood pressure, which, depending on the authority, is either greater than 130/85 mmHg or 140/90 mmHg.

Impaired Fasting Glucose (IFG): an intermediate, pre-diabetic state of glucose dysregulation defined by an elevated FPG concentration (≥100 and <126 mg/dl). This pathology has a high probability to advance to Type-2 Diabetes Mellitus and represents a component risk for CMD and mortality.

I**nsulin Resistance:** a pathological condition, considered a CMD component risk, in which cells fail to respond normally to the hormone insulin, resulting in elevated levels of blood glucose.

Interleukin (IL)-6: a secreted protein derived from T cells and macrophages that signals an immune response leading to inflammation.

Joint National Committee Guidelines for the Management of Hypertension in Adults (JNC-8): the most current (2014) evidence-based guidelines for the management of high blood pressure in adults.

Lipoproteins: a group of five soluble proteins that combine with and transport fat or other lipids in blood plasma. Lipoprotein classes are discriminated by their density, size and percentages of protein, cholesterol, phospholipid and

triacylglycerol & cholesterol esters, which define their atherogenicity. Classes include very low-density, intermediate-density, low-density and high-density lipoproteins.

Low-Density Lipoprotein Cholesterol (LDL-C): an atherogenic lipoprotein that serves as the major transporter of cholesterol in the blood. High levels pose a risk for all-cause CVD.

Mediterranean Diet: an array of nutritional plans considered traditional in Mediterranean countries; characterized by high consumption of vegetables and olive oil, and moderate consumption of protein.

mmHg: units of blood pressure measurement; millimeters of mercury

Non-Component CMD Risks: health hazards including physical deconditioning, imprudent nutrition and inflammation that contribute to CMD progression, but are not included among the CMD diagnostic risk components.

Obesity: a major component risk of CMD presenting as excessive body fat mass.

Oral Glucose Tolerance test (OGTT): A diagnostic test to determine the body's ability to dispose of an oral glucose load. Rates of glucose disposal from blood are used to diagnose the clinical states of diabetes or insulin resistance.

Osteopenia: lower-than-normal peak bone density, but not to a level considered osteoporosis; defined by T-scores ranging from -1 to -2.5 at the hip and spine, and resulting in bone fragility and increased risk of fracture.

Osteoporosis: lower-than-normal peak bone density; defined by T-scores less than -2.5 at the hip and spine, and resulting in bone fragility and increased risk of fracture.

Paraplegia: impairment or loss of motor and/or sensory function in the thoracic, lumbar or sacral (but not cervical) segments of the spinal cord, secondary to damage of neural elements within the spinal canal. With paraplegia, arm function is spared, but, depending on the level of injury, the trunk, legs, and pelvic organs may be involved. The term is used in referring to cauda equina and conus medullaris injuries, but not to lumbosacral plexus lesions or injury to peripheral nerves outside the neural canal.

Prediabetes: a condition characterized by slightly elevated blood glucose levels, regarded as indicative that a person is at risk of progressing to Type 2 diabetes.

SCI: Spinal Cord Injury

Statin: a class of FDA-approved prescription drugs used to reduce blood levels of low-density lipoprotein (LDL) cholesterol. Examples of approved single-action drugs in this class include atorvastatin, fluvastatin, lovastatin, lovastatin extended-release, pitavastatin, pravastatin, rosuvastatin and simvastatin.

Sympathomimetic Agents (also referred to as adrenergic drugs): stimulant compounds that mimic effects of endogenous agonists on the sympathetic nervous system; commonly used to treat hypotension and bronchoconstriction.

Systolic Blood Pressure (SBP): the maximum arterial pressure during the cardiac ejection phase.

Tetraplegia: impairment or loss of motor and/or sensory function in the cervical segments of the spinal cord due to damage of neural elements within the spinal canal. Tetraplegia results in impairment of function in the arms as well as typically in the trunk, legs, and pelvic organs, , including the four extremities. Tetraplegia does not include brachial plexus lesions or injury to peripheral nerves outside the neural canal.

Thiazide Diuretics: a class of pharmaceutical agents used to treat hypertension by inhibiting reabsorption of sodium (Na^+) and chloride (Cl^-) ions from the distal convoluted tubules in the kidneys. The result is a diuresis, volume depletion and lowering of blood pressure. Examples of single-action drugs are chlorothiazide, chlorthalidone, hydrochlorothiazide, methyclothiazide, and metolazone.

Triglycerides (TG): the primary constituent of stored and circulating fat in humans. Also, one of the two dyslipidemia risk components.

Tumor Necrosis Factor-alpha (TNF-α): a cell-signaling protein (cytokine) involved in central regulation of inflammation.

WHO: World Health Organization

Contents

Summary of Recommendations

The overall objective of this guideline is to improve the care of patients with spinal cord injury by guiding clinicians and policy makers with its recommendations. The following recommendations use available evidence and – where evidence is limited – Panel experience and consensus. The Panel based its evidence ratings primarily on research in which the focus of the study was SCI. This information was supplemented using evidence from trials, guidelines, and expert opinions contained in the scientific literature of non-SCI populations.

For individual patients, decisions are best made by considering these recommendations combined with clinical judgment, the latter based on specific knowledge about each patient's risk factors for cardiometabolic disease, the potential for adverse effects, and the availability of various options within one's center. The bracketed rating refers to the level of scientific evidence, the strength of the evidence, and the level of panel agreement with the recommendations.[1]

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[1] Nomenclature for Rating of Evidence and Strength of Panel Agreement

Levels of Scientific Evidence	
Level	**Description**
I	Evidence based on randomized controlled clinical trials (or meta-analysis of such trials) of adequate size to ensure a low risk of incorporating false-positive or false-negative results.
II	Evidence based on randomized controlled trials that are too small to provide level I evidence. These may show either positive trends that are not statistically significant or no trends and are associated with a high risk of false-negative results.
III	Evidence based on nonrandomized, controlled, or cohort studies; case series; case-controlled studies; or cross-sectional studies.
IV	Evidence based on the opinion of respected authorities or expert committees as indicated in published consensus conferences or guidelines.
V	Evidence that expresses the opinion of those individuals who have written and reviewed this guideline, based on experience, knowledge of the relevant literature, and discussions with peers.

Sources: Sackett, D.L. Rules of evidence and clinical recommendation on the use of antithrombotic agents. Chest 95 (2 Suppl) (1959): 2S-4S; and the U.S. Preventive Health Services Task Force, Guide to Clinical Preventive Services, 2nd ed. Baltimore: Williams and Wilkins, 1996.

Categories of the Strength of Evidence Associated with the Recommendations	
Category	**Description**
A	The guideline recommendation is supported by one or more Level I studies.
B	The guideline recommendation is supported by one or more Level II studies.
C	The guideline recommendation is supported by only one or more Level III, IV or V studies

Levels of Panel Agreement with the Recommendations	
Level	**Mean Agreement Score**
Low	1.0 to less than 2.33
Moderate	2.33 to less than 3.87
Strong	3.87 to 5.0

Summary of CMD and Component Risks Accompanying SCI

CMD

Recommendations:

1. Use the American Heart Association (AHA) definition, and the five constituent hazards of obesity, insulin resistance, dyslipidemia (including individual risks of low high-density lipoprotein cholesterol (HDL-C) and elevated Triglycerides (TG), and hypertension as CMD risk components for persons with SCI.

   (Scientific evidence: IV; Grade of recommendation: C; Level of Panel Recommendation: Strong)

2. Evaluate all adults with SCI for CMD at the time of discharge from rehabilitation. For those already discharged from rehabilitation, evaluate at the earliest opportunity.

   (Scientific evidence: V; Grade of recommendation: C; Level of Panel Recommendation: Strong)

Obesity

Recommendations:

1. Assess obesity beginning at the time of discharge from rehabilitation:

   A. Where possible, measure body composition using 3- or 4-compartment models to report obesity in adults with SCI until validated, clinically appropriate equations become available. Classify adult men with >22%BF and adult women with >35%BF as obese, and at high risk for CMD.

   B. When BMI is used as a surrogate marker for obesity in persons with SCI, BMI ≥22 kg/m2 is the cutoff point for obesity. Adult men and women with BMI ≥22 kg/m2 are at high risk for CMD.

      (Scientific evidence: III; Grade of recommendation: C; Level of Panel Recommendation: Strong)

2. Follow-up testing at least every three years following initial assessment when tests are normal in asymptomatic adults with SCI.

   (Scientific evidence: V; Grade of recommendation: C; Level of Panel Recommendation:Strong)

Impaired Fasting Glucose, Pre-Diabetes, and Diabetes

Recommendations:

1. Screen adults with SCI for diabetes and prediabetes, and repeat testing at least every three years if tests are normal.

   (Scientific evidence: IV; Grade of recommendation: C: Level of Panel Recommendation: Strong)

2. Adopt American Diabetes Association (ADA) guidelines to diagnose diabetes and pre-diabetes based on either fasting plasma glucose (FPG), the 2-hour plasma glucose (2-h PG) value after a 75-g OGTT, or A1C criteria.

   (Scientific evidence: IV; Grade of recommendation: C; Level of Panel Recommendation: Strong)

Hypertension

Recommendations:

1. Adopt AHA guidelines as the primary methods of assessment for BP measurement in persons with SCI. Blood pressure should be measured at every routine visit – and at least annually. Elevated BP readings should be confirmed on a separate patient visit to diagnose hypertension.

   (Scientific evidence: IV; Grade of recommendation: C; Level of Panel Recommendation: Strong)

2. Account for the unique challenges in making a diagnosis of hypertension in individuals with SCI, including postural influences and blood pressure variability due to autonomic instability.

   (Scientific evidence: III; Grade of recommendation: C; Level of Panel Recommendation: Strong)

Dyslipidemia

Recommendations:

1. Surveillance, in asymptomatic adults with SCI, of fasting LDL (estimated using the Friedewald equation105 when fasting TG levels are <200mg/dL, or, by direct measurement when higher), TC, TG, and HDL-C at least every three years when tests are first normal.

   (Scientific evidence: V; Grade of recommendation: C; Level of Panel Recommendation: Strong)

2. Annual screening of persons with SCI in the presence of multiple risk factors, or when evidence of dyslipidemia is confirmed or treatment initiated.

   (Scientific evidence: V; Grade of recommendation: C; Level of Panel Recommendation: Strong)

Summary of Management of CMD Risk Components after SCI

Lifestyle Intervention

Nutrition

Recommendations:

1. Caloric assessment using indirect calorimetry to estimate energy expenditure and assess energy needs.

   (Scientific evidence: III; Grade of recommendation: C; Level of Panel Recommendation: Strong)

2. Institute the following nutritional measures after the post-acute period:
   A. For all individuals, adopt a heart-healthy nutrition plan focusing on fruits, vegetables, whole grains, low-fat dairy, poultry, fish, legumes, non-tropical vegetable oils and nuts, while limiting sweets and sugar-sweetened beverages, and red meats.
   B. Adopt the Dietary Approach to Stopping Hypertension (DASH) nutritional plan or Mediterranean nutritional plan if hypertension or additional cardiometabolic risk factors are present.
   C. Limit saturated fat to 5-6% of total caloric intake.
   D. Limit daily sodium intake to ≤ 2400 mg for individuals with hypertension.

   (Scientific evidence IV; Grade of recommendation: C; Level of Panel Recommendation: Strong)

Physical Activity

Recommendation:

1. Individuals with SCI should participate in at least 150 minutes of physical exercise per week, according to their ability, beginning as soon as possible following acute spinal cord injury. The 150-minutes-per-week guideline can be satisfied by sessions of 30-60 minutes performed 3-5 days per week, or by exercising for at least three, 10-minute sessions per day. When individuals with SCI are not able to meet these guidelines, they should engage in regular physical activity according to their abilities and should avoid inactivity. They should consult their health-care provider about the amount and types of physical activity that are appropriate for their abilities.

   (Scientific evidence: IV; Grade of recommendation: C; Level of Panel Recommendation: Strong)

Pharmacotherapy and Surgery for Cardiometabolic Risk

Pharmacotherapy for Obesity

Recommendations:

1. Do not use FDA-approved prescription medications, nutraceuticals, and herbals for the management of obesity in persons with SCI.

   (Scientific evidence: V; Grade of recommendation: C; Level of Panel Recommendation: Strong)

2. Warn healthcare professionals and stakeholders with SCI about unsupervised use of over-the-counter and herbal anorexigenics, diuretics, and nutrient-uptake inhibitors for body fat or mass reduction.

   (Scientific evidence: V; Grade of recommendation: C; Level of Panel Recommendation: Strong)

Pharmacotherapy for Dysglycemia, Type-2 Pre-Diabetes, and Type-2 Diabetes

Recommendations:

1. Use a threshold of risk for HbA1c levels greater than 7%, which should be used as a criterion to emphasize lifestyle intervention.

   (Scientific evidence: IV; Grade of recommendation: C; Level of Panel Recommendation: Strong)

2. When glycemic targets are not met through lifestyle intervention, the selection of an anti-hyperglycemic agent (or agents) should conform to the most recent treatment guidelines.
   A. Metformin is the primary agent for treatment of HbA1c >7% unless contraindicated or poorly tolerated. If the maximum tolerated dosage of

metformin fails to achieve treatment goals, the addition of a second – and possibly a third agent – should conform to the most recent treatment guidelines.

B. Exercise caution when using multi-therapy approaches, which are more likely to precipitate hypoglycemia. Consideration should be paid to patient-specific characteristics where drug selection may invoke hypoglycemia, resting and postural hypotension, lymphedema, heart failure, and urinary tract infections.

C. Consider referral to an endocrinologist.

(Scientific evidence: IV; Grade of recommendation: C; Level of Panel Recommendation: Strong)

Pharmacotherapy for Dyslipidemia

Recommendations:

1. Exercise caution in the use of integrated cardiovascular risk equations for the selection of SCI patients for treatment with lipid-lowering therapies, due to the lack of calibration in SCI and the potential under-recognition of cardiovascular risk.

   (Scientific evidence: III; Grade of recommendation: C; Level of Panel Recommendation: Strong)

2. Patient selection for pharmacotherapy may be guided by other factors commonly seen in SCI, such as low levels of HDL-C and high levels of C-reactive protein. Statin monotherapy should be initiated using at least a moderate-intensity statin (e.g., rosuvastatin 10-20 mg/day).

   (Scientific evidence: III; Grade of recommendation: C; Level of Panel Recommendation: Strong)

Pharmacotherapy for Hypertension

Recommendations:

1. Apply evidence-based guidelines for treating hypertension in the general population of individuals with SCI. For most adults, a threshold for initiating pharmacological treatment and treatment target of 140/90 mm Hg is reasonable, although different targets may be considered in certain individuals and sub-populations.

   (Scientific evidence- IV; Grade of recommendation- C; Level of Panel Recommendation: Strong)

2. Consider SCI-related factors when selecting an antihypertensive agent, such as the effect of thiazide diuretics on bladder management.

   (Scientific evidence- IV; Grade of recommendation- C; Level of Panel Recommendation: Strong)

Bariatric Surgery for CMD Risk

Recommendations:

1. Bariatric surgery should only be considered as a last resort for persons with morbid obesity and spinal cord injury, due to the significant peri- and post-operative risks. If bariatric surgery is considered, an SCI specialist should provide preoperative, perioperative, and postoperative consultative services to the surgical and anesthesia teams to alert them to unique risks associated with SCI.

   (Scientific evidence: V; Grade of recommendation: C; Level of Panel Recommendation: Strong)

The Consortium of Spinal Cord Medicine

The Consortium of Spinal Cord Medicine is a collaboration of professional and consumer organizations with a common interest in healthcare for individuals living with spinal cord injury. The Consortium's mission is to direct the development and dissemination of evidence-based clinical practice guidelines (CPGs) and companion consumer guides. This mission is solely directed to improving the health care and quality of life for persons with SCI.

The Consortium is funded and administered by Paralyzed Veterans of America (Paralyzed Veterans). The Steering Committee, administratively supported by Paralyzed Veterans's Research and Education Department, is made up of one representative from each consortium-member organization.

Summary of Guidelines Development Process

The development of these guidelines involved the following major steps: creating a list of formal, key questions to be addressed, systematic searches of published literature related to these questions, critical appraisal of the quality of the retrieved studies, abstraction of relevant study results, creation of evidence-based recommendations, development of rationale that explain the recommendations, and review and agreement by panel members. The SCI Consortium's CPG development process also involved extensive field review and a legal review.

Funding and Potential Conflicts of Interest

Paralyzed Veterans contracted the literature searches and evidence reviews to an independent firm and provided administrative support for the process. Panel members received no compensation for their participation and declared all potential financial or other conflicts of interest.

Summary of Methods for CMD Diagnosis and CMD Risk Determination after SCI

Literature Search

A medical librarian searched Ovid MEDLINE® (1980 through September, Week 2 2015), the Cochrane Central Register of Controlled Trials® (1980 through September 22, 2015), Cochrane Health Technology Assessments (searched September 22, 2015), and the Cochrane Database of Systematic Reviews® (2005 through September 2015) using search terms related to chronic spinal cord injury. We also searched Ovid MEDLINE for names of authors known to have published in this area (on September 22, 2015). See the Appendix for complete search strategies. We attempted to identify additional studies through hand searches of reference lists of included studies and reviews. All citations were imported into an electronic database (Endnote® X7, Thomson Reuters).

Study Selection

Selection of included studies was based on the inclusion criteria created in consultation with Paralyzed Veterans. Two reviewers independently assessed titles and abstracts of citations identified through literature searches for inclusion, using the criteria below. Full-text articles of potentially relevant citations were retrieved and were assessed for inclusion by both reviewers. Disagreements were resolved by consensus. Results published only in abstract form were not included because inadequate details were available for quality assessment (risk of bias). Abstracts that had additional information available in slide sets from conference presentations, or those that provided supplemental data from published studies, were considered for inclusion.

Inclusion Criteria

In consultation with Paralyzed Veterans, 14 key questions were formulated relating to the prevalence of CMD and risk factors for disease, screening for CMD, CMD diagnosis methods, and the comparative effectiveness of treatment for CMD in the SCI population. Key questions 13 and 14 regarding CMD guidelines were not part of the systematic review, but they provide information on relevant guideline recommendations. Key questions and inclusion criteria are below.

Key Questions

Prevalence

1. What is the prevalence of individual CMD risk factors (e.g., obesity, glucose dysregulation, hypertension, dyslipidemia) in the SCI population?
2. What is the prevalence of CMD (defined as the presence of three or more risk factors) in the SCI population?
3. What is the prevalence of diabetes and cardiovascular disease in the SCI population?
4. What are the mortality rates from diabetes and diovascular disease in the SCI population?
5. What are the associations between CMD risk factors – alone or in clusters – and the development of diabetes and/or cardiovascular disease in the SCI population?

Screening

1. What is the evidence that screening for risk factors for diabetes and cardiovascular disease among asymptomatic adults with SCI improves health outcomes (e.g., myocardial infarction, amputation, mortality, quality of life)?
2. Which risk-factor screening methods or cutoffs are most effective in improving health outcomes in the SCI population?
3. Are there subgroups within the SCI population, based on demographic characteristics (e.g., age, gender, ethnicity, socioeconomic status, comorbidities [to include patients with known diabetes or known cardiovascular disease], medications, degree or level of paralysis, etiology of paralysis), for which screening for CMD risk factors are more or less effective in improving health outcomes?

Diagnosis

1. What is the diagnostic accuracy in the SCI population of fasting blood glucose or the glucose tolerance test for current diabetes, defined as having an HbA1c > 6.5 percent?
2. What is the diagnostic accuracy of CMD risk factors for current heart disease in the SCI population?

Treatment

1. What is the evidence that interventions to improve CMD risk factors – alone or in clusters – improves health outcomes in the SCI population?
2. Are there subgroups within the SCI population, based on demographic characteristics (e.g., age, gender, ethnicity, socioeconomic status, comorbidities [to include patients with known diabetes or known cardiovascular disease], medications, degree or level of paralysis, etiology of paralysis), for which interventions to improve CMD risk factors are more or less effective in improving health outcomes?

Guidelines

1. What are the existing CMD guidelines, or sections of guidelines, focusing on the SCI population?
2. What are the recommendations from major guideline groups for screening and interventions for CMD risk factors in patients without paralysis?

PICOTS

Population

Patients with nonacute, traumatic, or atraumatic irreversible spinal cord injury or dysfunction resulting in paralysis (excluding patients with spinal stroke)

Interventions

- Screening
  - Obesity
  - Glucose dysregulation
  - Hypertension
  - Dyslipidemia (e.g., low HDL, high TG)
  - Markers of inflammation (i.e., CRP, IL6, TNF-α)
- Treatment
  - Lifestyle modification
    - Diet
    - Exercise (i.e., active exercise and electrical stimulation)
    - Stress reduction
    - Education and counseling
  - Medication

Comparators

- Adults without SCI
- Another included intervention (head-to-head study in SCI population)
- Placebo
- Usual care

Outcomes

- Myocardial Infarction
- Stroke
- Amputation
- Blindness
- Chronic renal disease, including renal transplant)
- Peripheral vascular disease
- Pulmonary embolism or deep vein thrombosis
- Quality of life

Timing

- Chronic paralysis (paralysis of at least one year)

Setting

- Outpatient

Study Designs

- KQ 1-3: epidemiological database studies
- KQ 4: epidemiological database studies, case-control studies
- KQ 5-7: randomized trials, nonrandomized comparative studies (cohort, case-control)
- KQ 8-9: diagnostic accuracy studies where all participants received the gold standard
- KQ 10-11: randomized trials, nonrandomized comparative studies, case series
- KQ 12-13: guidelines

Data Abstraction

Information was abstracted on population characteristics, interventions, subject enrollment, prevalence, results for efficacy, effectiveness, and harms outcomes for trials, observational studies, and systematic reviews. When reported, intent-to-treat results were recorded. Data abstraction was performed by one reviewer and

independently checked by a second reviewer. Differences were resolved by consensus.

Validity Assessment (Risk of Bias)

We assessed the internal validity (risk of bias) of trials, observational studies, and systematic reviews based on predefined criteria. These criteria are based on the U.S. Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (United Kingdom) criteria[7–8] and the GRADE guidelines.[9] We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, blinding, the similarity of compared groups at baseline, loss to follow-up, and the use of intent-to-treat analysis. Trials that had a fatal flaw were rated at a high risk of bias, trials that met all criteria were rated at a low risk of bias, and the remainder were rated at a moderate risk of bias. As the moderate risk of bias category is broad, studies with this rating vary in their strengths and weaknesses. The results of some studies rated moderate risk of bias are likely to be valid, while others are only possibly valid. A fatal flaw is reflected by failure to meet combinations of items on the risk-of-bias checklist. An example would be a study with high attrition (e.g., 60%) combined with the inadequate handling of missing data, or one where details on randomization and/or allocation concealment were lacking, and there were baseline differences in important prognostic characteristics. Observational studies were rated on non-biased selection, loss to follow-up, pre-specification of outcomes, well-described and adequate ascertainment techniques, statistical analysis of potential confounders, and adequate duration of follow-up. Systematic reviews were rated on the clarity of review questions, the specification of inclusion and exclusion criteria, use of multiple databases and search for grey literature, sufficient detail of included studies, adequate assessment of the risk of bias of included studies, and adequate summarization of primary studies.

Two reviewers independently assessed the quality of each study and differences were resolved by consensus.

Grading the Quality of Evidence

We graded quality of evidence (QoE) based on the GRADE approach.[10–14]Developed to grade the overall quality of a body of evidence, this approach incorporates four key domains: risk of bias (includes study design and aggregate risk of bias), consistency, directness, and precision of the evidence. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, the strength of association (magnitude of effect), and publication bias.

Table 1 describes the grades of evidence that can be assigned. Grades reflect the quality of the body of evidence to answer key questions. Grades do not refer to the general efficacy or effectiveness of treatments, for example. Two reviewers independently assessed each domain for each outcome and differences were resolved by consensus.

The quality of the body of evidence was evaluated for each outcome by key question.

Table 1.

Definitions of the Grades of Overall Quality of Evidence

Grade	Definition
High	High confidence that the true effect lies close to that of the estimate of effect.
Moderate	Moderate confidence in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Limited confidence in the effect estimate. The true effect may be substantially different from the estimate of the effect.
Very Low	Very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. We reviewed studies using a hierarchy of evidence approach, where the best evidence is the focus of our synthesis for each question, population, intervention, and outcome addressed.

CMD: Definition and Risks Accompanying SCI

Section Preamble

The following section addresses hazards for CMD and its risk components in persons with SCI.

Panel Findings

- People with SCI have the same or greater degree of risk for CMD as the non-disabled population.
- Specific factors may elevate CMD risk, including veteran status, age at onset of SCI, duration of injury, pre-injury health status, family medical history, ethnicity, and heritage.
- The AHA's constituent CMD hazards of obesity, impaired fasting glucose, hypertension, and dyslipidemia (low HDL-C and elevated TG) are all considered risk components for CMD in persons with SCI.
- Risks of a sedentary lifestyle, excessive caloric and fat intake respective to energy needs, and elevated blood-borne inflammatory biomarkers may be considered as SCI-specific supplementary risks for CMD.

Rationale

CMD is a coalescing of interrelated cardiovascular, renal, metabolic, pro-thrombotic, and inflammatory health hazards,[1] and is recognized as a disease entity by the American Society of Endocrinology, the AHA, the International Diabetes Federation (IDF), the American Diabetes Association (ADA), and the World Health Organization (WHO).[2] The AHA and the National Institutes of Health (NIH) National Heart Lung Blood Institute (NHLBI) define CMD as the co-occurrence of any three of the medical hazards described in Table 2.

Table 2.

Guideline Definition of Cardiometabolic Disease		
Authority	**Diagnosis**	
AHA/NHLBI [3,12]	Three or more of:	Waist Circumference:* • Men — greater than 40 inches (102 cm) • Women — greater than 35 inches (88 cm)
		Plasma TG: ≥ 150 mg/dL (1.7 mmol/L)
		Reduced HDL ("good") cholesterol: • Men — Less than 40 mg/dL (1.03 mmol/L) • Women — Less than 50 mg/dL (1.29 mmol/L)
		Elevated blood pressure: ≥ 130/85 mm Hg or use of medication for hypertension
		Fasting glucose ≥100 mg/dL (5.6 mmol/L) or use of medication for hyperglycemia

*Note: Use of waist circumference is not validated in persons with SCI. Substitute definitions of obesity using: a: >22% BF body fat when using 3- or 4- compartment modeling, or b) BMI ≥ 22 kg/m^2.

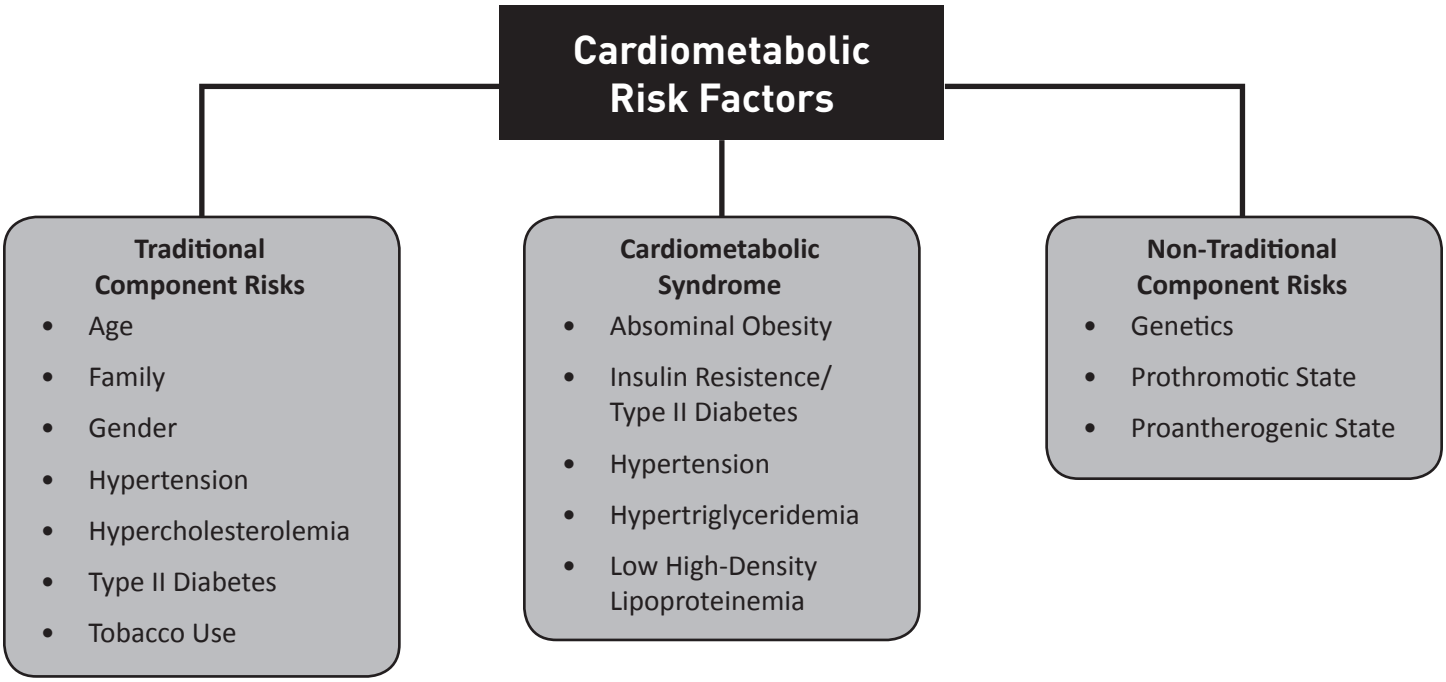
Abdominal (central) obesity, hypertension, hyperglycemia, hypertriglyceridemia, and low high-density lipoproteinemia.[3] While still lacking a fully harmonized diagnosis,[2] CMD is recognized to increase the probability of developing atherosclerotic disease, heart failure, and diabetes.[4–5] Prevalence in the U.S. is estimated at 34% of the non-disabled adult population[6] and is increasing with population aging. The CMD diagnosis confers a health risk equivalent to either the diagnosis of diabetes mellitus or extant coronary disease.

CMD is ultimately caused or worsened by a mismatch between energy consumption that is excessive in intake of kilocalories and saturated fats, and insufficient daily energy expenditure.[7] These risks are typically expressed through lifestyle factors reflecting poor compliance with optimal nutrition and an active lifestyle. The primary metabolic abnormality of CMD is insulin resistance, while the unified cause ensues excessive body mass, whose clinical feature is excessive visceral and ectopic fat. Inflammatory stress and endocrinopathies are not included among the AHA guideline risks, although both are recognized as either cause or consequence of the disorder.[8–9]

The prevalence of CMD reported in adults with SCI ranges from 31-72%, contingent on the number of possible risk factors included in the definition.[10–11] Depending on the study, this prevalence at least equals, and often exceeds, the CMD prevalence for the general population, which the Panel feels informs the SCI community about the risk that it poses.

Figure 1.

Interelated Component Risks of Cardiometabolic Disease.



CMD Component Risks Accompanying SCI

Section Preamble

The guideline component risks for CMD include obesity, insulin resistance, dyslipidemia, and hypertension. The following section addresses the hazards imposed by these individual risk components on the SCI population.

Obesity

Panel Findings

- Obesity (i.e., excessive adiposity) is a major risk component for CMD after SCI.
- Obesity after SCI is associated with risks of insulin resistance, diabetes, dyslipidemia, and hypertension.
- Obesity in persons with SCI is grossly underestimated when using both the surrogate marker of Body Mass Index (BMI) and criterion scores for obesity typically used for the general population.
- Guidelines that identify the conditions of overweight and obesity in non-disabled persons have limited application in diagnosing obesity in persons with SCI.

Rationale

"Obesity is a chronic, relapsing, neurochemical disease produced by the interaction of environment and host."[13] Emerging data suggests adipose tissue (especially visceral adiposity) and its associated connective tissue are the primary sources of systemic proinflammatory cytokines, vasoactive hormones and non-esterified fatty acids implicated in the development of dyslipidemia, insulin resistance, hypertension, and arteriosclerosis. Initially defined by the scientific community as >22% body fat (%BF) in men or >35%BF in women, the definition of obesity was changed to BMI ≥30 kg/m^2 by the WHO at the turn of the century to more easily capture large populations at risk for cardiovascular disease. [14]

Of the five AHA component risks, obesity after SCI has been most challenging to characterize and compare to non-SCI populations. BMI grossly underestimates obesity (overfat) in persons with SCI due to profound changes in fat-free mass (FFM), reflecting obligatory sarcopenia, osteopenia and reduced total body water associated with somatic and autonomic disruption of the spinal cord. The standard cutoff for BMI of >30 kg/m^2 grossly underestimates adiposity in persons with SCI, such that the true prevalence of CMD exceeds the 31-72% prevalence of CMD in persons with SCI reported in the literature.[11,15–16] Multiple studies have reported a BMI of 22-25 kg/m^2 in persons with SCI translates to >30% BF,[17–24] which is well above the standard cut-score for obesity of 22% BF in the non-SCI population. One study recalculated CMD prevalence with SCI-specific cutoff BMI≥22 kg/m^2, and found that doing so increased the range from 27-36% to 82-85% prevalence. [16]

For accurate obesity comparisons between persons with SCI and those without, BMI cutoffs for obesity of 22 kg/m^2 and 30 kg/m^2, respectively, should be used. Another option to determine overweight and obesity risk is waist circumference. However, the use of this proxy has not been validated in SCI populations and is likely inadequate as a surrogate obesity marker due to varying levels and neurological completeness of abdominal muscle paralysis.[25]

Insulin Resistance

Panel Findings

- The risk of insulin resistance, diabetes, or CMD in persons following SCI is at least as great as for persons without SCI.
- Race, ethnicity, veteran status, and family history may increase the risk of insulin resistance, diabetes, or CMD.

Rationale

The prevalence of diabetes in people with SCI varies with the attributes of the population being studied. Prevalence studies for diabetes in people with SCI in the U. S. have mostly been conducted with focus on U.S. veterans, so findings may not be generalizable to other populations.[26–28] U.S. studies report a higher prevalence of diabetes in people with SCI (16% to 33%) than those conducted in other countries (6% to 14%).[29–32] Evidence indicates that the prevalence of diabetes among U.S. veterans with SCI is not different from veterans without SCI.[26–27] However, moderate quality evidence from other countries indicates that persons with SCI have a higher prevalence of diabetes than able-bodied controls.[29–32] Traditional risk factors for diabetes and glucose intolerance in the general population, such as increasing age, at-risk race or ethnicity (Asian, African American, Hispanic, Native American, or Pacific Islander), and family

history of diabetes,[33] likely apply to the SCI population as well, though evidence specific to SCI is limited and of low quality.

Dyslipidemia

Panel Findings

- The prevalence of dyslipidemia among persons with SCI is high when based on established cholesterol guidelines and when compared to non-disabled individuals.
- The most consistent component of dyslipidemia risk among persons with SCI, when compared to non-disabled individuals, is depressed levels of HDL-C.

Rationale

The prevalence of dyslipidemia among persons with SCI is high when based on established cholesterol guidelines as well as comparisons to non-disabled individuals. Studies on lipid profiles reflecting higher cardiovascular risk among persons with SCI, compared to non-disabled individuals, have included the spectrum of lipid subfractions, including HDL-C, LDL-C, ratios of total cholesterol to HDL-C and LDL-C, and HDL/Apo-1 and Apo-A1/ApoB.[34–41] All these findings support the Panel's recommendations. The most consistent observation from studies assessing lipid profiles of persons with SCI is depressed HDL-C levels when compared to non-disabled individuals.[15,38,39,42–44] However, many of these studies lack specifics regarding which lipid abnormalities are observed, and their potential association with level and extent of the injury and other population characteristics. This disparity has led to variation in results between studies comparing cohorts of persons with SCI versus non-disabled controls. For example, in a large study comparing U.S. Veterans 65 years and older with subjects having SCI, ambulatory older Veterans, and ambulatory control subjects, no differences were observed in the prevalence of dyslipidemia (44%, 48, and 44%, respectively).[27] Conversely, in a Swedish cohort, the prevalence of dyslipidemia was markedly higher in persons with SCI than non-disabled controls (11% vs. 2%, $p<0.001$).[29] Studies have generally reported somewhat lower total cholesterol and HDL-C levels, but higher TG and a higher ratio of total cholesterol to HDL-C among SCI individuals compared with matched groups of non-SCI subjects.[34–39,43] Importantly, the overall prevalence of dyslipidemia in the general US population also tends to be high, and some research has questioned whether the prevalence of dyslipidemia is appreciably higher in persons with SCI (e.g., ≈50% of Americans have some form of lipid abnormality).[45] There is a lack of consistent data regarding the effects of level of injury as well as other clinical and demographic factors on the prevalence of dyslipidemia in persons with SCI.

Hypertension

Panel Findings

- The prevalence of hypertension in people with SCI varies with the attributes of the population being studied, including injury level, severity, and etiology.

Rationale

Reported prevalence of hypertension in people with SCI varies widely, ranging from 14% to 61%.[27,31,46–50] Age, gender, ethnicity, nationality, and other attributes of the population being studied may affect the reported prevalence, as may differences in methods to ascertain the presence of hypertension. Studies on the prevalence of hypertension in SCI in the United States[27,46–49] have mostly been conducted in U.S. veterans; findings may not be generalizable to other populations.

Injury to the spinal cord influences the regulation of blood pressure. Characteristics of the SCI, including neurological level and etiology of injury, may affect the prevalence of hypertension. Prevalence of hypertension is reported to be lower in people with tetraplegia compared with paraplegia, especially those with low paraplegia (T7 and below).[46–47,50] The odds of having hypertension were significantly lower in tetraplegic injuries, compared to matched controls without SCI in a study of U.S. veterans, while paraplegic injuries had similar odds of hypertension as controls. Veterans with non-traumatic SCI had higher odds of having hypertension compared with those with traumatic SCI after controlling for available SCI characteristics, age, demographics, and comorbidities.[46]

Supplementary CMD Risks Accompanying SCI

Section Preamble

The following section addresses the supplementary hazards associated with SCI that are population risk-relevant but not included among the AHA risk component hazards of CMD.

Physical Deconditioning

Panel Findings

- Individuals with SCI become physically deconditioned after injury.
- Physical deconditioning contributes to CMD and its risk determinants in persons with SCI.

Rationale

Exercise is a fundamental element in maintaining physical capacity and cardiovascular and metabolic health for persons of all ages and health states. The unified American College of Sports Medicine (ACSM) and WHO guidelines[51] prescribe exercise and provide physical activity guidelines for supporting health and wellness in the general population, which to the best of their abilities are also recommended for individuals with SCI.[52] These guidelines are in substantial agreement with both the ACSM Guidelines for Exercise Testing and Prescription[51] and also the Physical Activity Guidelines for Adults with SCI that were established for SCI Action Canada.[53] They are also similar to the Physical Fitness for Special Populations (PFSP) "Physical Fitness for Individuals with Spinal Cord Injury" recommendations of the American Physical Therapy Association.[54]

A sedentary lifestyle either imposed on or adopted by persons with SCI has long identified physical inactivity as a population health risk.[55] Notwithstanding a single identified cause for a sedentary lifestyle, a 1993 study reported that 1 in 4 healthy, young persons with SCI fail to satisfy a level of fitness needed to perform many essential activities of daily living.[56] More recently, it was reported that approximately 50% of patients with SCI report no leisure-time physical activity and 15% report leisure-time physical activity below the threshold required for meaningful health benefit (i.e., <1 hour/week).[57] This report implies that of the estimated 558,000 individuals currently living with SCI in the U.S., approximately 279,000 are completely sedentary and another 84,000 participate in a leisure-time physical activity considered inadequate to positively impact health.[58] While those with sensorimotor sparing of upper limb and trunk functions (i.e., paraplegia) have far greater capacities for physical activity and more extensive exercise options,[59] they are not necessarily more fit than persons with tetraplegia.[55,60]

While physical deconditioning per se is not included among the five component risks of CMD, it is linked with and considered a major cause of obesity, insulin resistance, hypertension, and dyslipidemia. Several factors, however, point to physical deconditioning after SCI as a major contributor to a CMD diagnosis. First, the SCI population was long ago identified at the lowest end of the human fitness continuum, making physical deconditioning suspect as a cause for CMD-related risks.[55,61–63] Second, a common finding after SCI is a low concentration of HDL-C,[36,40–41,64] which is known in persons without disability to be both cardioprotective and strongly linked with low levels of cardiorespiratory fitness.[65–67] Third, barriers to exercise participation are altogether common after SCI and may include self-imposed obstacles to exercise participation or legitimate physical barriers to exercise, lack of adapted exercise equipment, limited professional assistance, societal moirés, and financial limitations.[68–72]

Nutrition

Panel Findings

- Those with SCI who are beyond the post-acute period, especially individuals with higher level and severity of SCI, require fewer calories after SCI to maintain a stable body mass and composition than before the injury

Rationale

Following an acute SCI, body composition is altered by a significant loss of sublesional skeletal muscle, an increase in visceral fat mass,[1–4] and an injury-dependent decrease in sympathetic nervous system activity.[5] As a result, persons with SCI have decreased energy expenditure relative to energy intake, and when compared to individuals without SCI.[6–8] Subsequently, central (i.e., visceral) adiposity is common among persons with chronic SCI and is more prevalent than in persons without SCI. Importantly, the greatest increase in weight often occurs during the first year after injury.[9–15]

While physical activity has established benefits as a countermeasure to excessive caloric intake, some persons with SCI cannot substantially increase energy expenditure with physical activity alone. Some are limited by their level of injury[17] and overuse injuries[18–20] as well as other documented barriers to exercise.[21–24] Based on the existing evidence, and appreciating that caloric expenditure from activity rarely compensates for excessive caloric intake, dietary changes appear to be a more practical target for obesity management and CMD prevention in individuals with SCI.

Inflammation

Panel Findings

- CRP and other inflammatory biomarkers represent a unique subclinical risk component of CMD for the SCI population.
- The role of CRP and other inflammatory biomarkers in risk identification, development, and diagnosis of CMD and CMD risk components for the SCI population requires further exploration.

Rationale

Numerous markers of inflammation have been associated with cardiovascular disease (CVD) risk in non-disabled populations.[73] For example, in a study of nearly 28,000 post-menopausal women, high-sensitivity C-reactive protein (hs-CRP) was reported to be the strongest predictor of risk for cardiac events.[74] However, the relationship between inflammatory markers and CVD risk in SCI is complicated by the fact that these markers may be elevated due to higher fat mass, higher prevalence of urinary tract infections, pressure ulcers, and other factors inherent to SCI. Although inflammation has been shown to be elevated in persons with chronic SCI (even in the absence of acute infection), their relationship to CVD risk specifically in persons with SCI is not as clear as that in individuals without SCI.[34,75]

Studies comparing levels of inflammation between persons with SCI and age-matched non-disabled subjects have enrolled relatively small sample sizes, but they demonstrate a higher systemic inflammatory state when compared to non-disabled subjects. Liang and colleagues[15] studied 129 men from the National Health and Nutrition Examination Survey (NHANES) with SCI who were free of infection, matching them by age and race to a group of non-disabled subjects. SCI subjects were more likely to have elevated CRP (odds ratio 2.29), and CRP was higher in complete versus incomplete injury (median 3.7 mg/L vs. 1.2 mg/L, p=0.005). The elevation in CRP was independent of age, smoking, physical activity, waist circumference, and weight, but was associated with low HDL. Lee and colleagues[76] examined the relationship between hs-CRP, insulin resistance, and metabolic syndrome among 93 individuals with chronic SCI. Metabolic syndrome and insulin resistance were present in nearly one-quarter of the SCI sample (22.6%). Subjects with fasting insulin resistance had significantly higher mean hsCRP (4.29±3.25 mg/L) than those who were not insulin resistant (2.24±2.02) ($p<0.05$). Moreover, hsCRP was significantly elevated in individuals who presented with high CVD risk including severe dyslipidemia (≥4 abnormal lipid values) and elevated Framingham Risk scores (≥6).

Although CRP is the most studied and widely recognized inflammatory marker, other proinflammatory cytokines have been evaluated in SCI. These biomarkers have important roles in the early stages of inflammation and the immunoregulatory process. Wang et al.[77] compared 62 men with traumatic, complete SCI and no active infection with 29 age-matched, ambulatory control subjects. Irrespective of injury level and duration, subjects with SCI had consistently higher levels of serum CRP (4.0±2.7 vs. 1.4±1.1 mg/L) and interleukin-6 (IL-6). Also, these higher levels of inflammation were independent of dyslipidemia and insulin resistance. Frost et al.[78] compared serum levels of CRP and cytokine levels between 37 subjects with chronic SCI and 10 healthy non-disabled control subjects. SCI subjects had higher levels of serum CRP but not IL-6 or tumor necrosis factor alpha (TNF-α). No associations were observed due to age or duration of injury. Davies et al.[79] compared 56 SCI subjects with 35 age-matched, non-disabled controls and reported that SCI subjects exhibited serum concentrations of IL-6, TNF-α, and IL-1RA that were greater than non-disabled subjects. Elevated cytokine concentrations were not associated with high white blood cell counts, level of injury, or American Spinal Injury Association impairment classification.

CRP has been shown to be elevated in acute and chronic SCI subjects with and without urinary tract infections, suggesting that it may be more attributable to an underlying disease state rather than the SCI itself. While studies have consistently shown higher than normal CRP levels in persons with SCI, few data are available regarding the relationship between CRP and CVD risk, specifically in SCI.[79] Among individuals with SCI who are insulin resistant and display components of the CMD, hsCRP is elevated, suggesting a clinically important association with CVD risk in this population. Lee et al.[79] reported that CRP was significantly associated with the presence of other well-known CVD risk factors, including metabolic syndrome, insulin resistance, and elevated Framingham risk. Similarly, Gibson et al.[80] reported that persons with SCI had CRP

levels consistent with high CVD risk and that those with high CRP had larger waist circumference, BMI, percent fat mass, and HOMA-IR values than those with lower CRP. Epidemiological studies are lacking regarding the association between inflammation in SCI and outcomes; thus, the role of CRP and other inflammatory markers in the development of atherosclerosis and predicting future CVD events in the SCI population requires further exploration.

Methods for CMD Diagnosis, and CMD Risk Identification and Surveillance Intervals after SCI

Section Preamble

The following section provides recommendations for measurement and the criterion scores for CMD and CMD risk determination in persons with SCI. A recommended schedule for surveillance and follow-up on CMD is shown in Table 3.

Table 3.

Recommended Schedule for Identification/Follow-Up of Cardiometabolic Risk after SCI				
Risk	**Test**	**Patients**	**Initial**	**Follow-Up**
CMD	3+ risk components (see below)	All	At discharge from rehabilitation	Annually
CMD Risk Components				
Impaired Fasting Glucose, Pre-Diabetes and Diabetes	FPG, OGTT, or A1C	Asymptomatic individuals with SCI having one or more risk factors	FBG annually; Other tests at a minimum of three-year intervals if tests are normal	
Obesity	Multi-compartment modeling or BMI	Individuals having confirmed pre-diabetes, diabetes, or CMD		Annual testing and ongoing management
Dyslipidemia	Fasting lipid panel preferred, but at minimum HDL-C and TG	All	At discharge from rehabilitation	Annual testing, or when evidence of elevated risk is identified
Hypertension	Blood pressure			Measured at every routine visit (and at least annually). Elevated BP readings should be confirmed on a separate visit to diagnose hypertension.
Lifestyle Risk Factors				
Suboptimal Nutrition	Maintenance of stable body- fat mass or whole-body mass throughout the lifespan	All	Medically supervised nutrition plan beginning in rehabilitation, or as soon as possible	Continuous throughout the lifespan
Physical Deconditioning	Exercise testing if practical	All, insofar as feasible and practical	Recommendations for therapeutic or recreational exercise initiated by the time of rehabilitation discharge	Annual with continuous follow-up throughout the lifespan

CMD

Recommendations

1. The AHA definition should be used, and constituent hazards of obesity, insulin resistance, dyslipidemia (low HDL-C and elevated TG), and hypertension should be included as CMD risk components for persons with SCI.

   (Scientific evidence: IV; Grade of recommendation: C; Level of Panel Recommendation: Strong)

2. All adults with SCI should be evaluated for CMD at the time of discharge from rehabilitation. For those who are already discharged from rehabilitation, evaluate at the earliest opportunity.

   (Scientific evidence: V; Grade of recommendation: C; Level of Panel Recommendation: Strong)

Rationale

The recommended standard is a "sum of risks" guideline that defines CMD as three or more of the five individual risk determinants.[2] Other standards are published but are not necessarily harmonized. The recommendation provides a baseline for future comparison of CMD and its risk component risks.

Obesity

Recommendations

1. Obesity should be assessed beginning at discharge from rehabilitation:

   A. Where possible, measure body composition using 3- or 4-compartment models to report obesity in adults with SCI, until validated, clinically appropriate equations become available. Classify adult men with >22%BF and adult women with >35%BF as obese, and at high risk for CMD.

   B. When BMI is used as a surrogate marker for obesity in persons with SCI, BMI ≥22 kg/m^2 is the cutoff point for obesity. Adult men and women with BMI ≥22 kg/m^2 are at high risk for CMD. (Scientific evidence: III; Grade of recommendation: C; Level of Panel Recommendation: Strong)

2. Follow-up testing should be performed at least every three years following initial assessment when tests are normal in asymptomatic adults with SCI.

   (Scientific evidence- V; Grade of recommendation: C; Level of Panel Recommendation: Strong)

Rationale

BMI grossly underestimates obesity (overfat) in persons with SCI due to profound changes in fat-free mass (FFM), reflecting obligatory sarcopenia, osteopenia, and reduced total body water associated with somatic and autonomic disruption of the cord. Multiple studies have reported BMI of 22-25 kg/m^2 in persons with SCI translates to >30%BF,[81–91] well above the standard cut-score for obesity of 22%BF in the non-SCI population.

For accurate obesity comparisons between persons with SCI and those without, BMI cutoffs for obesity of 22 kg/m^2 and 30 kg/m^2, respectively, should be used. Unfortunately, such comparisons have not been reported. Rather, most studies have used a BMI cutoff of 25 kg/m^2 to reflect "overweight or obese" in both SCI and non-SCI populations. Of eight studies that reported the prevalence of being overweight or obese in persons with SCI, i.e., BMI>25 kg/m^2, a 53-60% prevalence rate was noted.[15,49,92–97] Conversely, obesity rates in the general population (BMI>30 kg/m^2) range between 20-27%.[49,94–95,97] In the three studies that compared BMI>25 kg/m^2 in persons with SCI and non-SCI controls, results were mixed, with one showing a lower prevalence in SCI,[93] and the other two showing no significant difference in prevalence between SCI and controls.[96,98]

Impaired Fasting Glucose, Pre-Diabetes, and Diabetes

Recommendations

1. Adults with SCI should be screened for diabetes and prediabetes, with repeat testing at least every three years if tests are normal.

   (Scientific evidence: IV; Grade of recommendation: C; Level of Panel Recommendation: Strong)

2. ADA guidelines should be adopted to diagnose diabetes and pre-diabetes based on either FPG, the 2-hour plasma glucose (2-h PG) value after a 75-g OGTT, or A1C criteria.

   (Scientific evidence: IV; Grade of recommendation: C; Level of Panel Recommendation: Strong)

Rationale

Testing for diabetes and prediabetes in asymptomatic individuals in the general population has been recommended for those with one or more risk factors and beginning at age 45 for those without additional risk factors, with repeat testing at three-year intervals at least if tests are normal.[99] Lower physical activity, and changes in body composition with reduced lean muscle mass and increased percentage of body fat, may contribute to the additional risk of glucose intolerance and insulin resistance in individuals with SCI.[100–101] Directly measuring insulin resistance is difficult and unstandardized, making it impractical for the clinical setting, but FPG is an acceptable indirect test. Alternatively, an OGTT or HbA1c can be used. While specific evidence for an optimal screening interval or age to start screening individuals with SCI is currently lacking, it is reasonable to consider screening in adults with SCI and to repeat testing at one- to three-year intervals if tests are normal.

Standards of Medical Care in Diabetes published by the ADA outline methods and criteria for identifying Type 2 pre-diabetes and diabetes (Table 4).[99] Criteria for the diagnosis of diabetes include either FPG >126 mg/dL (7.0 mmol/L) after no caloric intake for at least 8 h, or 2-h PG >200 mg/dL (11.1 mmol/L) during an OGTT with the test performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water, or A1C >6.5% (48 mmol/mol). In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose >200 mg/dL (11.1 mmol/L) is also considered diagnostic of diabetes in the general population; however, in SCI this could be confusing since such symptoms, including polyuria, polydipsia, weight loss, and fatigue, often have other etiologies.

Criteria for identifying prediabetes include either FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG), 2-h PG in the 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT), or A1C 5.7 to 6.4% (39 to 47 mmol/mol). For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range (Table 4).

Table 4.

Criteria for the Diagnosis of Pre-Diabetes and Diabetes

Criterion	Pre-Diabetes	Diabetes
A1C	5.7-6.4%	≥ 6.5%
FPG	100-125 mg/dL (95.6-6.9 mmol/L)	≥126 mg/dL (7.0 mmol/L)
OGTT	140-199 mg/dL (7.8-11.0 mmol/L)	≥ 200 mg/dL (11/.1 mmol/L)*
RPG		≥ 200 mg/dL (11/.1 mmol/L)#

*In the absence of unequivocal hyperclycemia, results should be confirmed by repeat testing.

#Only diagostic in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis.

A1C: Glycated Hemoglobin; FPG: Fasting Plasma Glucose, OGTT: Oral Glucose Tolerance Test (2 hour, 75g Glucose); RPG: Random Plasma Glucose

Hypertension

Recommendations

1. AHA guidelines should be adopted as the primary methods of assessment for BP measurement in persons with SCI. Blood pressure should be measured at every routine visit and at least annually. Elevated BP readings should be confirmed on a separate patient visit to diagnose hypertension.

   (Scientific evidence: IV; Grade of recommendation: C; Level of Panel Recommendation: Strong)

2. Unique challenges should be considered in making a diagnosis of hypertension in individuals with SCI, including postural influences and blood pressure variability due to autonomic instability.

   (Scientific evidence: III; Grade of recommendation: C; Level of Panel Recommendation: Strong)

Rationale

The AHA Scientific Statement on Recommendations for Blood Pressure Measurement in Humans[102] is the most current AHA authority on BP measurement procedures, selection of devices, and device calibration. The BP goals are consistent with AHA/NHLBI Guidelines on the diagnosis of CMD.[1,2]

Posture may affect blood pressure in people with SCI, especially those with tetraplegia. A study of veterans with SCI reported differential orthostatic effects on systolic hypertension based on the level of injury. Prevalence of systolic blood pressure (SBP) ≥140 mmHg was lower in the supine compared to the seated position in subjects with low paraplegia, whereas the incidence of a supine SBP ≥140 mmHg was increased by 53% compared to seated in subjects with tetraplegia.[48] The presence of supine hypertension may be missed in individuals with tetraplegia if only seated blood pressure is measured. Supine hypertension may be associated with lack of a nocturnal dip in blood pressure, which has been associated with cardiovascular risk in the general population.

Significant variability in blood pressure is common in people with SCI due to autonomic instability,[47,103] so single blood pressure readings may be especially inaccurate to determine the presence and degree of hypertension in this population. Coexisting conditions such as autonomic dysreflexia and orthostatic hypotension may contribute to diagnostic confusion, particularly in individuals with tetraplegia. Episodic blood pressure elevation should prompt the consideration of autonomic dysreflexia in individuals with SCI at or above the T6 neurological level.[104] Repeating blood pressure measurements over time and measuring blood pressure in both the supine and seated positions, with documentation of the position in which blood pressure was recorded, may improve the accuracy of diagnosing hypertension after SCI.

Dyslipidemia

Recommendations

1. Asymptomatic adults with SCI should be surveilled for fasting LDL (estimated using the Friedewald equation105 when fasting TG levels are <200mg/dL, or, by direct measurement when higher), TC, TG and HDL-C at least every three years when test results are first normal.

   (Scientific evidence: V; Grade of recommendation: C; Level of Panel Recommendation: Strong)

2. Persons with SCI should be annually screened in the presence of multiple risk factors, or when evidence of dyslipidemia is confirmed or treatment initiated.

   (Scientific evidence: V; Grade of recommendation: C; Level of Panel Recommendation: Strong)

Rationale

A fasting lipid profile provides the most comprehensive method for detection of dyslipidemia risk. Screening guidelines for dyslipidemia in the non-disabled population vary by age, with treatment goals personalized according to risk levels. (AACE 2017 Tables 6 and 11).[106] However, the decision to screen should always be based on clinical judgment. Specific indications – notably patient age, age at SCI, clinical evidence of existing disease, family history, and the presence of other co-morbid CMD risks – should alert physicians to conduct screenings. As all-cause vascular disease is reported to be accelerated after SCI, the risk for earlier CMD components risk and CMD diagnosis should be taken into consideration.[7,107]

The linkage of major risks for obesity and low HDL-C,[108] and reports that BMI is among the strongest risk predictors for diabetes[109–110], compel the attention of both obesity and insulin- resistance once presenting in persons with SCI. Moderate TG elevations (≥150 mg/dL) may identify individuals at risk for the insulin resistance and levels ≥200 mg/dL may detect individuals at substantially increased ASCVD risk, making their co-morbidity a concern once identified. Current guidelines do not consider an isolated finding of low HDL sufficient to initiate drug therapy, but at a minimum this foretells the need for diligent lifestyle intervention. [111]

Moreover, recent guidelines from the AACE106 emphasize the strong association between low HDL-C and hypertriglyceridemia, T2DM, overweight or obesity, physical inactivity, cigarette smoking, very high carbohydrate intake, and genetic factors. Low HDL-C can thus act synergistically with other lipid risk factors to increase clinical risk, making low HDL a sentinel of risk, even in the presence of low TC and very low (< 70 mg/dL) LDL-C.[112]

Management of CMD Risk Components After SCI

Section Preamble

The following section will present findings and recommendations for management of CMD and CMD risk determinants through lifestyle intervention (i.e., nutrition and physical activity), pharmacotherapy, and surgery. Panel recommendations are summarized in Table 5.

Table 5.

<table>
<tr><th colspan="4">Guideline Definition of Cardiometabolic Disease</th></tr>
<tr><th rowspan="2">CMD Risk</th><th rowspan="2">Goal</th><th colspan="2">Primary Management: Lifestyle Intervention</th></tr>
<tr><th>Nutrition</th><th>Exercise</th></tr>
<tr><td>CMD Diagnosis</td><td>Reduce the number of risk components to < 3</td><td rowspan="5">Institute the following nutritional adjustments beginning as soon as possible after the SCI:

1. For all individuals, adopt a heart-healthy nutrition plan focusing on fruits, vegetables, whole grains, low-fat dairy, poultry, fish, legumes, non-tropical vegetable oils, and nuts, while limiting sweets and sugar-sweetened beverages, and red meats;

2. Adopt the DASH nutritional plan or Mediterranean nutritional plan if hypertension or additional cardiometabolic risk factors are present;

3. Limit saturated fat to 5-6% of total caloric intake; and

4. Limit daily sodium intake to ≤ 2400 mg for individuals with hypertension.</td><td rowspan="5">Encourage at least 150 minutes per week of moderate-intensity physical exercise beginning as soon as possible following acute spinal cord injury. The 150-minute-per-week guideline can be satisfied by sessions of 30-60 minutes performed three to five days per week, or by exercising for at least three, 10-minute sessions per day</td></tr>
<tr><td>Overweight or Obese</td><td>Reduce body fat mass to achieve a BMI ≤ 22 kg/m^2</td></tr>
<tr><td>Insulin Resistance, Pre-Diabetes, or Diabetes</td><td>Reduce FBG to ≤100 mg/dL and HbA1c < 7%</td></tr>
<tr><td>Dyslipidemia</td><td>Reduce TG to ≤ 150 mg/dL and increase HDL-C to ≥ 40mg/dL (male) and ≥ 50 mg/dL (female)</td></tr>
<tr><td>Hypertension</td><td>Reduce BP-STOLIC to < 130 mmHg and BP-DIASTOLIC to < 85 mmHg</td></tr>
</table>

Guideline Definition of Cardiometabolic Disease (cont.)		
Risk	**Goal**	**Secondary Management: Pharmacotherapy**
CMD Diagnosis	As above	Treat specific CMD risk component
Overweight or Obese		None recommended
Insulin Resistance, Pre-Diabetes, or Diabetes		Metformin (Glucophage) as the first-line agent for treatment of HbA1c >7%, unless contraindicated or poorly tolerated. If the maximum tolerated dose of Metformin fails to achieve goals, add a second and possibly a third agent, according to ADA Standards of Medical Care (2015).
Dyslipidemia		Patient selection for pharmacotherapy should be guided by other factors commonly seen in SCI, such as low levels of HDL-C and high levels of C-reactive protein. Statin monotherapy should be initiated using at least a moderate-intensity statin (e.g., rosuvastatin 10-20 mg/day).
Hypertension		JNC 8 guidelines recommend initial antihypertensive treatment with a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB) in the non-black population, and either a thiazide-type diuretic or CCB in the black population.

LIFESTYLE INTERVENTION

Nutrition

Recommendations

1. When establishing caloric targets, all persons with SCI should undergo a caloric assessment using indirect calorimetry to estimate energy expenditure and assess energy needs.

   (Scientific evidence: III; Grade of recommendation: C; Level of Panel Recommendation: Strong)

2. The following nutritional measures should be instituted after the post-acute period:

   A. All individuals should adopt a heart-healthy nutrition plan focusing on fruits, vegetables, whole grains, low-fat dairy, poultry, fish, legumes, non-tropical vegetable oils, and nuts, while limiting sweets, sugar-sweetened beverages, and red meats.

   B. The DASH nutritional plan or Mediterranean nutritional plan should be adopted if hypertension or additional cardiometabolic risk factors are present.

   C. Saturated fat should be limited to 5-6% of total caloric intake.

   D. Daily sodium intake should be limited to ≤ 2400 mg for individuals with hypertension.

   (Scientific evidence: IV; Grade of recommendation: C; Level of Panel Recommendation: Strong)

Rationale

Following an acute SCI, body composition is altered by a significant loss of skeletal muscle, an increase in fat mass,[113–116] and in some cases a decrease in sympathetic nervous system activity.[117] As a result, persons with SCI have decreased whole-body energy expenditure compared to individuals without SCI,[118–120] and a mismatch between excessive intake and expenditure. Subsequently, central adiposity is common among persons with chronic SCI and is more prevalent than in persons without SCI. Importantly, the greatest increase in weight often occurs during the first year post-injury when caloric intake is excessive relative to expenditure.[17,121–126]

While physical activity has established benefits as a countermeasure to excessive caloric intake some persons with SCI cannot effectively balance energy intake and expenditure with physical activity alone. Some are limited by their level of injury[56] and overuse injuries[127–129] as well as other documented barriers to exercise.[70–71,130–131] Based on the existing evidence, and appreciating that caloric expenditure from physical activity rarely compensates for excessive caloric intake, nutritional modification may represent a more practical and effective target for obesity management and CMD prevention in individuals with SCI. The panel does not recommend a single nutritional plan but notes success in weight loss using the Mediterranean diet in the Diabetes Prevention Program,[132–133] and the

DASH Diet, which may be more effective for hypertension management.[134] The Healthy Mediterranean-Style Pattern is also adapted from the Healthy U.S.-Style Pattern, modifying amounts recommended from some food groups to more closely reflect eating patterns that have been associated with positive health outcomes in studies of Mediterranean-style diets.

Prospective evaluation of weight loss programs in the SCI population has been limited. Weight loss programs designed for the non-disabled population may not be appropriate for the specific health[135–139] and nutritional needs[140–144] of the SCI population. A pilot study of a weight loss program consisting of education on nutrition, exercise, and behavioral modification in individuals with chronic SCI who were overweight or obese resulted in weight loss and improvements in dietary intake.[145] This study utilized the Time-calorie displacement diet, which emphasizes large intakes of high bulk, low energy-density foods such as fruits and vegetables, high-fiber grains, and cereals. It also emphasized a moderate intake of high energy-density foods such as meats, cheeses, sugars, and fats.[146]

Physical Activity

Panel Findings

- Individuals with SCI become physically deconditioned after injury.
- Physical deconditioning is associated with a frank diagnosis of CMD or clinical progression of its risk determinants.

Recommendation

1. All individuals with SCI should participate in at least 150 minutes per week of a physical exercise, according to their ability, beginning as soon as possible following acute spinal cord injury. The 150-minutes-per-week guideline can be satisfied by sessions of 30-60 minutes performed three to five days per week, or by exercising for at least three, 10-minute sessions per day. When individuals with SCI are not able to meet these guidelines, they should engage in regular physical activity, according to their abilities, and should avoid inactivity. They should consult their health-care provider about the amounts and types of physical activity that are appropriate for their abilities.

   (Scientific evidence: IV; Grade of recommendation: C; Level of Panel Recommendation: Strong)

Rationale

Persons with SCI occupy the lowest end of the human fitness continuum.[55,62] Reduction of fitness after SCI is attributable to various factors including inactivity imposed by diminished active muscle contraction, the need for special equipment and assistance performing exercise, physical and financial barriers, pain, and injury.[72,147]

Engagement in routine physical exercise and activity is known to improve fitness,[148–152] reduce the risk of developing CMD component and non-component conditions, and diminish pathogenicity of CMD component risks severity after diagnosis.[153–154] Several prospective and cross-sectional studies in persons with SCI have identified a benefit for physical deconditioning in managing selected CMD component risks. These studies mirror studies in the general population that have more extensively identified these benefits and identified exercise as an effective lifestyle plan in both healthy individuals and those with chronic diseases.[155]

Authoritative guidelines for exercise after SCI have already been established.[156–157] The panel recommendations mirror these guidelines, including the U.S. Department of Health and Human Services Physical Activity Guidelines for Individuals with Disabilities.

PHARMACOTHERAPY AND SURGERY FOR CARDIOMETABOLIC RISK

Preamble

The following section provides recommendations for drug therapy addressing specific CMD risk components and surgical countermeasures to CMD in persons with SCI.

Pharmacotherapy for Obesity

Panel Findings

- Insufficient evidence to support the use of prescription and non-prescription anti-obesity agents for either short-term or long-term use by persons with SCI.
- A need for broadened surveillance and treatment of obesity starting soon after injury, and, for all individuals with SCI, emphasizing patient-centered therapeutic lifestyle change incorporating exercise and nutritional modification where these recommendations have not been implemented.

Recommendations

1. FDA-approved prescription medications, nutraceuticals, and herbals should not be used for the management of obesity in persons with SCI.

   (Scientific evidence: V; Grade of recommendation: C; Level of Panel Recommendation: Strong)

2. Healthcare professionals and stakeholders with SCI should be warned about the unsupervised use of over-the-counter and herbal anorexigenics, diuretics, and nutrient uptake inhibitors for body fat or mass reduction.

   (Scientific evidence: V; Grade of recommendation: C; Level of Panel Recommendation: Strong)

Rationale

Pharmacological agents, nutraceuticals, and herbal medicines are currently used as alternatives to, or in combination with, behavioral modification, nutritional adjustments, exercise, and surgery to treat obesity. All FDA-approved medications are recommended as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in obese adults, or, overweight patients having at least one weight-related comorbid condition, such as hypertension, type-2 diabetes, or dyslipidemia.[158] The following are FDA-approved drugs for treating obesity and overweight:

Orlistat is a potent gastrointestinal lipase inhibitor that reduces dietary fat absorption by approximately 30%. It has not undergone testing for safety, tolerance, or effectiveness in persons with SCI. While the efficacy of orlistat for long-term weight loss has been reported in several RCTs,[159–160] a meta-analysis incorporating five studies of 11,000 participants found common gastrointestinal side effects including diarrhea, fecal incontinence, oily spotting, flatulence, bloating, and dyspepsia.[161–162] Stringent dietary management focusing on the restriction of fat intake must be undertaken to lessen, but not necessarily eliminate, these risks. *The Panel feels that use of the drug in persons with a neurogenic bowel, autonomic dysreflexia, and insensate skin may be significantly disrupting, socially distressing, and potentially hazardous.*

Phentermine/topiramate is a multitherapy pharmaceutical containing a low-dose of the centrally acting appetite suppressant phentermine and the antiepileptic agent topiramate. This combination has been shown to be effective for the long-term treatment of obesity,[163–164] although topiramate is unlicensed as monotherapy for obesity. The efficacy, tolerance, and safety of this combination drug have not undergone testing in persons with SCI. Phentermine is a sympathomimetic agent that is FDA-approved for up to three months administration but not longer-term use. Sympathomimetic properties pose risks for insomnia, xerostomia, dizziness, palpitation, hand tremor, and elevation of blood pressure and pulse rate.[165–166] Topiramate is an anti-seizure agent that may have additive effects for other analeptics, such as those used for neuropathic pain. Tricyclic antidepressants and serotonin reuptake inhibitors potentiate effects of phentermine and have major adverse interactions with phentermine/topiramate. *The Panel feels that use of this agent in persons with SCI who have altered function of the autonomic nervous system and who may be taking other medications that interact with phentermine/topiramate is potentially hazardous.*

Bupropion/naltrexone is a multitherapy drug containing naltrexone, a synthetic opioid antagonist, and bupropion, an aminoketone antidepressant. The combination has not undergone testing for safety, tolerance, or effectiveness in persons with SCI. In two published clinical trials[167–168] the most commonly reported adverse drug events for bupropion/naltrexone sustained release were related to the gastrointestinal system. Nausea was reported in 27%-34% of participants, with an increased risk associated with a higher dosage of the naltrexone component. A headache was reported more often in treatment groups (14% to 24% of participants) than in placebo groups. In both clinical trials, the dose-dependent adverse events of constipation (15%–24%), dizziness (7%–14%), and xerostomia (8%) were higher with the study drug than placebo. There is a potential for interactions with many drug agents, including benzodiazepines, analeptics, and antidepressants. *The Panel feels that use of this agent in persons with SCI who have neurogenic bowel, autonomic dysreflexia and who may be taking other medications that may interact with bupropion/naltrexone is potentially hazardous.*

Lorcaserin is a 5-hydroxytryptamine (5-HT2C) selective agonist that primarily acts on the hypothalamus to suppress appetite.[169]

Stimulation of the 5-HT2C receptor may lead to hallucinations, euphoria, or altered mood. Caution is recommended for the use of lorcaserin by individuals with mild-moderate renal dysfunction. As a serotonin agonist, potential interactions may occur with medications that affect serotonergic pathways. The risk of serotonin syndrome and neuroleptic malignant syndrome-like reactions can occur if lorcaserin is used in combination with other serotonergic agents, although these effects have not been studied on persons with an SCI. Interactions can be expected with serotonin-norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, tricyclic antidepressants, aminoketone antidepressants, triptans for migraine headaches, tryptophan, dextromethorphan, lithium, tramadol, and drugs used for bipolar disorders.[170] *The Panel feels that use of this agent in persons with SCI who have a neurogenic bladder, renal dysfunction, autonomic dysreflexia and who may be on other medications that may interact with lorcaserin is potentially hazardous.*

In summary, none of the drugs prescribed for treating obesity have undergone extensive clinical testing for safety, tolerance, and effectiveness in the SCI population. All have adverse effects that may substantially affect the overall health, daily function, safety, and comfort of people with SCI. The described agents have extensive drug-drug interactions with agents contained within the pharmacopeia that are typically used to treat SCI. Lifestyle intervention using diet and exercise is an alternative that is deemed by the Panel to be as effective as, and safer than, drug therapies. For these reasons, the Panel feels the medical and social risks of drug use in persons significantly outweigh reported benefits on mass body reduction or cardiovascular disease risk abatement.

Pharmacotherapy for Dysglycemia, Type-2 Pre-Diabetes, and Type-2 Diabetes

Panel Findings

- A need for broadened surveillance and treatment of dysglycemia after SCI, while first emphasizing patient-centered therapeutic lifestyle change incorporating behavior, exercise, and nutrition modification where these recommendations have not been implemented.

Recommendations

1. A threshold of risk for HbA1c level greater than 7% should be used as a criterion to emphasize lifestyle intervention.

   (Scientific evidence: IV; Grade of recommendation: C; Level of Panel Recommendation: Strong)

2. When glycemic targets are not met through lifestyle intervention, selection of an anti-hyperglycemic agent or agents should conform to the most recent treatment guidelines.

   A. Metformin should be the primary agent for treatment of HbA1c >7% unless contraindicated or poorly tolerated. If the maximum tolerated dosage of metformin fails to achieve treatment goals, the addition of a second and possibly a third agent should conform to the most recent treatment guidelines.

   B. Caution should be exercised when using multi-therapy approaches, which are more likely to precipitate hypoglycemia. Consideration should be paid to patient-specific characteristics where drug selection that may invoke hypoglycemia, resting and postural hypotension, lymphedema, heart failure, and urinary tract infections.

   C. Referral to an endocrinologist should be considered.

   (Scientific evidence: IV; Grade of recommendation: C; Level of Panel Recommendation: Strong)

Rationale

Lowering of non-gestational HbA1C with a target of <7% in adults slows microvascular progression of diabetes, and, if implemented soon after the diabetes diagnosis and sustained for the long-term, results in a modest reduction of macrovascular disease. The more conservative A1C goal of <6.5% is preferred for individuals without significant hypoglycemia or other treatment adverse effects.[171] These patients may include those with short duration of diabetes, suitable treatment results accompanying lifestyle or metformin monotherapy, long life expectancy, or absence of significant CVD.

The panel recommendations are in substantial agreement with the Pharmacologic Therapy for Type 2 Diabetes: Synopsis of the 2017 American Diabetes Association Standards of Medical Care in Diabetes (2017),[172] which recommend the following:

- Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacologic agent for the treatment of type 2 diabetes.
- Long-term use of metformin may be associated with biochemical vitamin B12 deficiency, and periodic measurement of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy.
- Consider initiating insulin therapy (with or without additional agents) in patients with newly diagnosed type 2 diabetes who are symptomatic and/or have A1C ≥10% (86 mmol/mol) and/or blood glucose levels ≥300 mg/dL (16.7 mmol/L).
- If noninsulin monotherapy at maximum tolerated dose does not achieve or maintain the A1C target after three months, add a second oral agent, a glucagon-like peptide-1 receptor agonist, or basal insulin.
- A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include efficacy, hypoglycemia risk, impact on weight, potential side effects, cost, and patient preferences.
- For patients with type 2 diabetes who are not achieving glycemic goals, insulin therapy should not be delayed.
- In patients with long-standing, sub-optimally controlled type 2 diabetes and an established atherosclerotic cardiovascular disease, empagliflozin or liraglutide should be considered as they have been shown to reduce cardiovascular and all-cause mortality when added to standard care. Ongoing studies are investigating the cardiovascular benefits of other agents in these drug classes.

General warnings for GI complications and volume depletion accompany metformin monotherapy, which may be more impactful on persons with SCI and include risks of resting and orthostatic hypotension. A greater risk of hypoglycemia should be anticipated with multitherapy approaches, especially when incorporating sulfonylureas and basal insulin as second-line agents. Risks for genitourinary infection, volume depletion, and resting and orthostatic hypotension may be more pronounced in persons with SCI than the general population and should be judiciously monitored.

Pharmacotherapy for Dyslipidemia

Panel Findings

- A need for broadened surveillance and treatment of dyslipidemia in SCI, while first emphasizing therapeutic lifestyle change, including exercise and nutritional modification where these recommendations have not already been implemented.
- A threshold of cardiovascular risk or LDL-C for the initiation of statin therapy has not been established in SCI.
- Assessment of postprandial lipemia/remnant cholesterol and inflammation (C-reactive protein) may contribute to the detection of SCI patients with risk related to dyslipidemia.

Recommendations

1. Caution should be employed in the use of integrated cardiovascular risk equations for the selection of SCI patients for treatment with lipid-lowering therapies, due to the lack of calibration in SCI and the potential under-recognition of cardiovascular risk.

   (Scientific evidence: III; Grade of recommendation: C; Level of Panel Recommendation: Strong)
2. Patient selection for pharmacotherapy may be guided by other factors commonly seen in SCI, such as low levels of HDL-C and high levels of C-reactive protein. Statin monotherapy should be initiated using at least a moderate-intensity statin (e.g., rosuvastatin 10-20 mg/day).

   (Scientific evidence: III; Grade of recommendation: C; Level of Panel Recommendation: Strong)

Rationale

Selection of patients for treatment of dyslipidemia is often based on the use of cardiovascular risk equations developed for use by non-disabled populations, and therefore with uncertain generalizability and calibration to populations with SCI.[107,173] In particular, most risk equations, except the Reynolds Risk Score, do not account for the inflammation/lipid interaction and do not incorporate the risk associated with remnant particles or postprandial lipemia.[174–175] Given these limitations, typical thresholds for the initiation of pharmacologic treatment of dyslipidemia, developed in non-disabled populations, may not apply to SCI. This finding is significant, as only approximately 25% of patients with SCI meet conventional criteria for the initiation of lipid-lowering therapy.[176–177]

Data are sparse on the rates of treatment and control of dyslipidemia in SCI, with available evidence suggesting that a therapeutic gap is present,[176,178] consistent with data from the National Health and Nutrition Examination Survey in non-disabled persons. Lifestyle intervention for dyslipidemia most effectively incorporates exercise training, which has been shown to reduce LDL-C by up to 25% and increase HDL-C by 10%.[179] Otherwise, the use of traditional therapeutic agents potentially effective in SCI-associated dyslipidemia include statins, fibric acid derivatives, and niacin. Statin drugs are effective for dyslipidemia and are demonstrated to reduce the risk of cardiovascular outcomes. Most randomized controlled trials conducted in non-disabled individuals selected subjects by LDL-C. However, recent data from the Heart Outcomes Prevention Evaluation-3 study (HOPE-3) show significantly lower rates of nonfatal cardiovascular events irrespective of LDL-C.[180] In this study, patients without known cardiovascular disease were selected for treatment with rosuvastatin 10 mg daily based on the presence of a cardiovascular risk factor to include low HDL-C, or elevated waist-to-hip ratio (common factors seen in SCI). Similarly, selection of patients for treatment using rosuvastatin 20 mg/d based on the presence of elevated levels of subclinical inflammation (C-reactive protein ≥2mg/L) when LDL-C is not elevated (<130 mg/dL) is reasonable based on the results of the JUPITER trial.[181] Limited outcomes data in patients with SCI suggest that statins may reduce all-cause mortality.[182] Once initiated, statin therapy should be monitored in accordance with the product information per the Food and Drug Administration. A notable exception may be for heightened surveillance for myopathy using creatine kinase monitoring due to the limitations to assessing pain and weakness in the SCI population. There are no outcomes data in the treatment of dyslipidemia in SCI using non-statin therapies, such as niacin or fibric acid derivatives. Niacin tolerably improves the dyslipidemic risk profile in SCI.[183] Fibrates (gemfibrozil, bezafibrate) also improve the dyslipidemia risk profile and reduce cardiovascular outcomes in nondisabled dyslipidemic patients.

Pharmacotherapy for Hypertension

Panel Findings

- The Panel finds insufficient evidence to support a different threshold than the general population for treating high blood pressure in individuals with spinal cord injury.

Recommendations

1. Evidence-based guidelines for treating hypertension in the general population should be used to treat individuals with SCI. For most adults, a threshold for initiating pharmacological treatment and treatment target of 140/90 mm Hg is reasonable, although different targets may be considered in certain individuals and sub-populations.

   (Scientific evidence: IV; Grade of recommendation: C; Level of Panel Recommendation: Strong)

2. SCI-related factors should be considered when selecting an antihypertensive agent, such as the effect of thiazide diuretics on bladder management.

   (Scientific evidence: IV; Grade of recommendation: C; Level of Panel Recommendation: Strong)

Rationale

Abundant evidence from randomized, controlled trials in the general population has shown the benefit of antihypertensive drug treatment in improving important health outcomes in people with hypertension. Baseline blood pressure is often lower in people with tetraplegia and high paraplegia than in the general population, but evidence to support a different threshold for treating high blood pressure in individuals with spinal cord injury is lacking. The Panel recommends also applying evidence-based guidelines for treating hypertension in the general population to those with SCI. Current guidelines for initiating pharmacological treatment for hypertension by most major organizations recommend 140/90 mm Hg as the threshold for pharmacological treatment and target goal for most adults with hypertension. However, there are differences and areas of controversy regarding treatment thresholds and targets for certain sub-populations between the different guidelines. For example, in age cut-off for a higher systolic BP target and treatment threshold, a lower BP threshold is recommended by some organizations for certain populations, including those with diabetes or chronic kidney disease.[184–187]

The Eighth Joint National Committee (JNC 8) evidence-based guideline for the management of high blood pressure in adults recommends initiating pharmacological treatment to lower blood pressure at systolic blood pressure (SBP) of 140 mm Hg or higher or diastolic blood pressure (DBP) of 90 mm Hg or higher in adults under 60 years, and in all adults with diabetes or chronic kidney disease regardless of age, and at SBP of 150 mm Hg or higher or DPB of 90 mm Hg or higher in adults age 60

or higher without diabetes or chronic kidney disease.[184] Guidelines from the American College of Physicians and the American Academy of Family Physicians (ACP/AAFP) recommend the same threshold for initiating treatment and target goal as JNC 8 for adults aged 60 or older.[185] The American Society of Hypertension and the International Society of Hypertension (ASH/ISH) guidelines for management of hypertension have similar treatment threshold and target goals as the JNC 8 guidelines, except for a higher age cut-off (80 years or older versus 60 years) for using a 150 mm Hg SBP target instead of 140 mm Hg in adults without diabetes or chronic kidney disease.[186] A science advisory from the AHA, the American College of Cardiology (ACC), and the Centers for Disease Control and Prevention(CDC) specifies that for most adults the BP goal is less than 140/90; however, lower targets may be appropriate for some populations. [187]

Consistent with the above guidelines, the Panel recommends initiating pharmacological treatment to lower blood pressure at SBP of 140 mm Hg or higher or DBP of 90 mm Hg or higher in most adults with SCI. While the Panel recognizes differences in treatment goals and targets for certain sub-populations between various guidelines, it does not endorse a specific guideline over the others given the current lack of high-quality evidence to make that determination. For individual patients, clinicians should use a combination of factors to set BP goals, including scientific evidence, clinical judgment, and patient tolerance. In some patients, including those with albuminuria, chronic kidney disease, or additional cardiovascular risk factors, clinicians could consider a lower BP target (for example 130/80 mm Hg) if lower targets can be achieved without undue treatment burden, while recognizing that the benefit of pursuing these targets levels using antihypertensive drugs is currently not established through RCTs.

Evidence-based guidelines for choosing antihypertensive medications in the general population are based on randomized controlled trials studying comparative benefit and harm of different agents on specific health outcomes. JNC 8 guidelines recommend initial antihypertensive treatment with a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB) in the non-black population, and either a thiazide-type diuretic or CCB in the black population.[184] In adults with chronic kidney disease, initial or add-on antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes. Additional co-existing conditions may influence drug selection. For example, in those with a history of myocardial infarction, a beta-blocker and ARB/or ACEI are indicated regardless of blood pressure.186

Studies to systematically test antihypertensive agents in people with SCI are lacking. In the absence of such evidence, it is reasonable to apply guidelines for choosing antihypertensive agents in the general population to people with SCI. However, SCI-related factors may affect the choice of an antihypertensive agent in some circumstances. For example, a thiazide-type diuretic may not be the antihypertensive agent of choice in individuals who perform intermittent bladder catheterizations, because of its effect on increased urine volumes between catheterizations. Hyponatremia, hypokalemia, or decline in renal function sometimes occur during the first nine months of thiazide use, and older patients may be especially vulnerable to renal-electrolyte disturbances, gout, hyperglycemia, and hypotension.

The main objective of hypertension treatment is to attain and maintain goal blood pressure. JNC 8 guidelines recommend increasing the dose of the initial drug or adding a second drug if goal blood pressure is not reached within a month of initiating treatment.[184] An ACEI and an ARB should not be used together in the same patient. If goal BP cannot be achieved with two drugs, a third drug should be added and titrated. A study by Barry et al. found that veterans with traumatic SCI were less likely to be prescribed more than one antihypertensive medication when compared with matched controls 46. The authors postulated that these findings could relate to concern over the propensity of these patients to develop hypotension. While some patients with SCI who have co-existing orthostatic hypotension and supine hypertension require careful titration and trial of medications, clinicians should continue to assess blood pressure and adjust the treatment regimen until goal blood pressure is reached.

In those with treatment-resistant hypertension, compliance and adherence to treatment regimen should be confirmed. Clinician empathy increases patient trust, motivation, and adherence to therapy. Drug interactions (e.g., nonsteroidal anti-inflammatory drugs, illicit drugs, sympathomimetic agents, over-the-counter drugs and herbal supplements) may hamper blood pressure control and should be considered. Secondary causes of hypertension should be investigated. Referral to a hypertension specialist may be appropriate for those whose blood pressure cannot be controlled with the above strategies.[186]

Self-monitoring of BP should be encouraged for most patients with hypertension. System-level strategies should be considered to improve hypertension treatment, including: identifying all patients eligible for management, monitoring at the practice level, increasing patient and provider awareness, systematic follow-up of patients for

the initiation and maintenance/intensification of therapy, clarifying roles of healthcare providers to implement a team approach, and reducing barriers for patients to receive and adhere to medications.[187]

BARIATRIC SURGERY FOR CMD RISK

Panel Findings

- The evidence fails to support bariatric surgery for obesity management after SCI, except in cases of last resort.

Recommendations

1. Bariatric surgery should only be considered as a last resort for persons with morbid obesity and spinal cord injury, due to the significant peri- and post-operative risks.

    A. If bariatric surgery is considered, an SCI specialist should provide preoperative, perioperative and post-operative consultative services to the surgical and anesthesia teams to alert them to unique risks associated with SCI.

    (Scientific evidence: V; Grade of recommendation: C; Level of Panel Recommendation: Strong)

Rationale

There have been no Level I, II or III studies investigating bariatric surgery to manage obesity in persons with SCI. Of the few case reports in the literature, none speak of the unique perioperative or post-operative risks of the procedure in this special population.[188–190] Current guidelines for determining bariatric surgery candidates and their perioperative/post-operative care in Europe and the United States utilize BMI and screening practices suitable to the non-SCI population,[191–192] but do not address the complex care needs/risks associated with SCI, including but not limited to paralysis, mobility and activities of daily living deficits, neurogenic bradycardia, neurogenic hypotension, adapted myocardial atrophy, circulatory hypokinesis, risk for autonomic dysreflexia, neurogenic restrictive and obstructive lung disease, neurogenic bladder, neurogenic bowel, neurogenic skin, sarcopenia, osteopenia/osteoporosis, and spasticity. While the odds ratio for venous thromboembolism in SCI after bariatric surgery has recently been determined as 5.71 (95% CI 1.36-24.02) based on 83 individuals with paraplegia in a total sample of [91,963,193] other potential complications associated with such surgeries, including abdominal pain/cramping, dumping syndrome, beriberi, post-operative adhesions and loose stools have not been characterized or reported.

Directions for Future Research

1. In general, additional and larger population-based trials assessing risk and interventions that are discriminated by key levels of injury are needed.
2. Multicenter and central database studies should focus on hard endpoints, such as event rates of diabetes, myocardial infarction, stroke, and death, as well as component risks of CMD.
3. More targeted post-mortem determinations and retrospective chart reviews should be used to assess CMD as a cause of death after SCI.
4. Given their unique physiology, guideline-supported interventions derived from the general population should be assessed for safety and efficacy in persons with SCI.
5. Studies that rank-order CMD component risks for the SCI population should be undertaken so that hazards may be aggressively addressed. Emphasis should be directed toward early post-injury obesity and diabetes prevention.
6. The role of autonomic dysfunction and autonomic dysreflexia in disease progression and risk determination requires additional study.
7. The population hazards for non-traditional, population-specific risk factors should be better determined, including inflammatory biomarkers, physical deconditioning, the human microbiome, and others.
8. Subpopulation risk assessments based on race, gender, pre-injury risks, and unique subpopulations – including veterans – are needed to discriminate risk, identification, and management.
9. Population-specific risk prediction equations that model after Framingham should be studied, and modified if possible, for the SCI population to forecast future risks for all-cause events and death.
10. Big data descriptions of CMD prevalence (i.e., using electronic health records, Veteran's Health Administration, private or public insurance data, etc.) should be pursued.
11. Randomized trials of screened/unscreened populations and controlled interventions are needed within the SCI population.
12. Determine the cost-effectiveness of aggressive surveillance and early intervention for CMD risk and diagnosis among people with SCI.
13. Education initiatives should target primary care providers and consumers with greater knowledge of CMD identification, treatment initiation, and management in this population.
14. Population-specific prediction equations for energy expenditure need to be developed and validated.
15. Identification of population-specific pharmacotherapy and related treatment benefits, risks, and all-cause burdens are required to better understand and implement best practice.
16. Imaging and phenotypic assessments should be targeted to develop and optimize integrated risk markers and tools for early screening and detection of CMD.

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Appendix 1: Search Strategies

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to September Week 2 2015>

Search Strategy

1. (spine or spinal) adj3 injury adj10 (risk or epidemiology or etiology or death or dying or die or dies or died or fatal$ or mortality or dead or prognosis or develop or diagnose adj5 (cardio or cardiac or heart or myocardial or coronary or vascular or cerebrovascular or stroke or arrhythmia or dysrhythmia or tachycardia or fibrillation).mp. [Mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (124)
2. (spine or spinal) adj3 injury adj10 ((risk or epidemiology or etiology or death or dying or die or dies or died or fatal or mortal or dead or prognosis or develop or diagnose) adj5 (diabetes or prediabetes or metabolic syndrome or hypergly or (elevate or high or impair) adj3 glucose).mp. (12)
3. (spine or spinal) adj3 injury adj10 (risk or epidemiology or etiology or death or dying or die or dies or died or fatal or mortality or dead or prognosis or develop or diagnose) adj5 (hyper cholesterol or hyper lipid or hyperlipoprotein or syndrome x or metabolic x or metabolic syndrome or (elevate or high or impair) adj3 (blood pressure or cholesterol or triglyceride or lipid or ldl or hdl or lipoprotein).mp. (3)
4. 1 or 2 or 3 (136)
5. limit 4 to humans (122)
6. (risk or epidemiology or etiology or death or dying or die or dies or died or fatal or mortality or dead or prognosis or develop or diagnose) adj5 (cardio or cardiac or heart or myocardial or coronary or vascular or cerebrovascular or stroke or arrhythmia or dysrhythmia or tachycardia or fibrillation).mp. (393469)
7. (risk or epidemiology or etiology or death or dying or die or dies or died or fatal$ or mortality or dead or prognosis or develop or diagnose) adj5 (diabetes or prediabetes or metabolic syndrome or hypergly or (elevated or high or impair) adj3 glucose).mp. (89564)
8. ((risk$ or epidemiology or etiology or death or dying or die or dies or died or fatal or mortality or dead or prognosis or develop or diagnose) adj5 (hypercholesterol or hyperlipid or hyperlipoprotein or syndrome x or metabolic x or metabolic syndrome$ or ((elevate or high or impair) adj3 (blood pressure or cholesterol or triglyceride or lipid or ldl or hdl or lipoprotein).mp. (20110)
9. exp Spinal Cord Injuries/co, mo, pp [Complications, Mortality, Physiopathology] (18118)
10. 6 or 7 or 8 (467939)
11. 9 and 10 (261)
12. 5 or 11 (327)
13. limit 12 to yr="1980 -Current" (322)
14. limit 13 to (english language and humans) (282)
15. paralysis/ (18776)
16. exp paraplegia/ (11965)
17. Quadriplegia/ (7322)
18. exp Spinal Cord injuries/ (40009)
19. exp Spinal Cord/ (83825)
20. (adverse or complicate) adj7 (paralysis or paraplegia or hemiplegia or quadriplegia or tetraplegia).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (4852)
21. (immobilize or "bed ridden" or bedridden or (unable or inability or incapable or ((lack or lost or lose or loses or losing or "not") adj3 (able or capable or capacity or function) adj5 (move or moving or motion or stand or walk).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (88132)

22. 20 or 21 (92955)
23. 19 and 22 (760)
24. 15 or 16 or 17 or 18 or 23 (71342)
25. exp Cardiovascular Diseases/ (1995414)
26. exp glucose metabolism disorders/ (355816)
27. exp Metabolic Diseases/ (793674)
28. exp Nutritional Physiological Phenomena/ (420655)
29. 27 or 28 (1162438)
30. exp Cardiovascular System/ (1066819)
31. exp Cardiovascular Physiological Phenomena/ (832930)
32. exp Diagnostic Techniques, Cardiovascular/ (689995)
33. 30 or 31 or 32 (1872616)
34. 29 and 33 (105865)
35. exp lipids/bl (194095)
36. exp glucose/bl (36)
37. 25 or 26 or 34 or 35 or 36 (2419181)
38. 24 and 37 (7257)
39. limit 38 to (english language and humans) (5052)
40. exp epidemiologic factors/ (1241122)
41. exp Epidemiologic Methods/ (4758797)
42. exp Epidemiologic Studies/ (1823426)
43. exp Prognosis/ (1204739)
44. exp risk/ (916612)
45. exp vital statistics/ (719473)
46. 40 or 41 or 42 or 43 or 44 or 45 (5498853)
47. 39 and 46 (1807)
48. limit 47 to yr.="1980 -Current" (1702)
49. limit 48 to (english language and humans) (1702)
50. 48 not 14 (1599)
51. (spine or spinal) adj3 injury adj7 (cardio or cardiac or heart or myocardia or coronary or vascular or cerebrovascular or stroke or arrhythmia or dysrhythmia or tachycardia or fibrillation). mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1544)
52. (spine or spinal) adj3 injury adj7 (diabetes or prediabetes or metabolic syndrome or metabolism) adj2 (profile or response or reflex or react or function or dysfunction or alter or impair) or hyperglycemia or (elevated or high or impair) adj3 glucose). Mp. (185)
53. (spine or spinal) adj3 injury adj7 (hypercholesterol or hyperlipid or hyperlipoprotein or syndrome x or metabolic x or metabolic syndrome or (elevated or high or impaired) adj3 (blood pressure or cholesterol or triglyceride or lipid or LDL or HDL or lipoprotein). mp. (31)
54. (spine or spinal) adj3 injury adj7 (hemodynamic or baroreflex or metaboreflex or circulation or vasoconstriction) adj3 (response or reflex or react or function or dysfunction or alter or impair). Mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (58)
55. (spine or spinal) adj3 injury adj7 (obesity or adiposity or body fat or (abdominal adj2 fat) or body mass index or bmi or body composition or body measures).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (109)
56. (spine or spinal) adj3 injury adj5 (physiopathology or pathophysiology).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (235)
57. (spine or spinal) adj3 injury adj7 (c-reactive protein or c-rp or crp or interleukin 6 or interleukin six or il-6 or tissue necrosis factor alpha or tissue necrosis factor a or tnf-alpha or tnf-a)).mp. (69)
58. (spine or spinal) adj3 injury adj7 (thrombosis or embolism or blood clot).mp. (334)
59. 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 (2441)
60. limit 59 to yr.="1980 -Current" (2319)
61. limit 60 to (english language and humans) (1718)
62. 61 not 50 (1434)
63. 14 or 50 or 62 (3174)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <August 2015>

Search Strategy:

1. (paraplegia or quadriplegia or tetraplegia or hemiplegia or (chronic or permanent) adj3 (paralysis or sci or (spine or spinal) adj3 injury) adj7 (cardio or cardiac or heart or myocardial or coronary or vascular or cerebrovascular or stroke or arrhythmia or dysrhythmia or tachycardia or fibrillation).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (699)
2. (paraplegia or quadriplegia or tetraplegia or hemiplegia or (chronic or permanent) adj3 paralysis or sci or (spine or spinal) adj3 injury adj7 (diabetes or prediabetes or metabolic syndrome or metabolism) adj2 (profile or response or reflex or react or function or dysfunction or alter$ or impair$)) or hypergly$ or (elevated or high or impaired) adj3 glucose). mp. (19)
3. (paraplegia or quadriplegia or tetraplegia or hemiplegia or (chronic or permanent) adj3 paralysis or sci or (spine or spinal) adj3 injury) adj7 (hypercholesterol or hyperlipid or hyperlipoprotein or syndrome x or metabolic x or metabolic syndrome or (elevate or high or impaired) adj3 (blood pressure or cholesterol or triglyceride or lipid or ldl or hdl or lipoprotein). mp. (6)
4. (paraplegia or quadriplegia or tetraplegia or hemiplegia or (chronic or permanent) adj3 paralysis or sci or (spine or spinal) adj3 injury) adj7 (hemodynamic or baroreflex or metaboreflex$ or (circulation or vasoconstriction) adj3 (response or reflex or react or function or dysfunction or alter or impair). mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (7)
5. adj3 injury) adj7 (obese or adipose or body fat or abdominal fat or body mass index or bmi or body composition or body measure). mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (15)
6. (paraplegia or quadriplegia or tetraplegia or hemiplegia or (chronic or permanent) adj3 paralysis or sci or (spine or spinal) adj5 (physiopathology or pathophysiology). mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (28)
7. (paraplegia or quadriplegia or tetraplegia or hemiplegia or (chronic or permanent) adj3 paralysis or sci or (spine or spinal) adj7 (c-reactive protein$ or c-rap or crp or interleukin 6 or interleukin six or il-6 or tissue necrosis factor alpha or tissue necrosis factor a or tnf-alpha or tnf-a). mp. (7)
8. (paraplegia or quadriplegia or tetraplegia or hemiplegia or (chronic or permanent) adj3 paralysis or sci or (spine or spinal) adj7 (thrombosis or embolus or blood clot). mp. (45)
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (802)
10. limit 9 to (yr.="1980 -Current" and english language) (488)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to August 2015>

Search Strategy:

1. (paraplegia or quadriplegia or tetraplegia or hemiplegia or (chronic or permanent) adj3 paralysis or sci or (spine or spinal) adj7 (cardio or cardiac or heart or myocardia or coronary or vascular or cerebrovascular or stroke or arrhythmia or dysrhythmia or tachycardia or fibrillation). mp. [mp=title, abstract, full text, keywords, caption text] (83)
2. (paraplegia or quadriplegia or tetraplegia or hemiplegia) or (chronic or permanent) adj3 paralysis or sci or (spine or spinal) adj7 (diabetes or prediabetes or metabolic syndrome or (metabolism adj2 (profile or response or reflex or reaction or function or dysfunction or alter$ or impair) or hyperglycemia or (elevated or high or impair) adj3 glucose). mp. (9)
3. (paraplegia or quadriplegia or tetraplegia or hemiplegia or (chronic or permanent) adj3 paralysis or sci or (spine or spinal) adj7 (hypercholesterol or hyperlipid or hyperlipoprotein or syndrome x or metabolic x or metabolic syndrome or (elevated or high or impaired) adj3 (blood pressure or cholesterol or triglycerides or lipid or LDL or HDL or lipoprotein). mp. (1)
4. (paraplegia or quadriplegia or tetraplegia or hemiplegia or (chronic or permanent) adj3 paralysis or sci or (spine or spinal) adj7 (hemodynamic or baroreflex or metaboreflex or (circulation or vasoconstriction) adj3 (response or reflex or reaction or function or dysfunction or alter or impair). mp. [mp=title, abstract, full text, keywords, caption text] (1)

5. (paraplegia or quadriplegia or tetraplegia or hemiplegia or (chronic or permanent) adj3 paralysis or sci or (spine or spinal) adj7 (obese or adipose or body fat or (abdomen adj2 fat) or body mass index$ or bmi or body composition or body measure). mp. [mp=title, abstract, full text, keywords, caption text] (1)
6. (paraplegia or quadriplegia or tetraplegia or hemiplegia or (chronic or permanent) adj3 paralysis or sci or (spine or spinal) adj3 injury) adj5 (physiopathology or pathophysiology). mp. [mp=title, abstract, full text, keywords, caption text] (1)
7. (paraplegia or quadriplegia or tetraplegia or hemiplegia or (chronic or permanent) adj3 paralysis or sci or (spine or spinal) adj7 (c-reactive protein$ or c-rp or crp or interleukin 6 or interleukin six or il-6 or tissue necrosis factor alpha or tissue necrosis factor a or tnf-alpha or tnf-a)). mp. (1)
8. (Paraplegia or quadriplegia or tetraplegia or hemiplegia or (chronic or permanent) adj3 paralysis or sci or (spine or spinal) adj7 (thrombosis or embolus or blood clot). mp. (6)
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (94)

Database: EBM Reviews - Health Technology Assessment <3rd Quarter 2015>

Search Strategy:

1. (paraplegia or quadriplegia or tetraplegia or hemiplegia or (chronic or permanent) adj3 paralysis or sci or (spine or spinal) adj7 (cardio or cardiac or heart or myocardial or coronary or vascular or cerebrovascular or stroke$ or arrhythmia or dysrhythmia or tachycardia or fibrillation). mp. [mp=title, text, subject heading word] (2)
2. (paraplegia or quadriplegia or tetraplegia or hemiplegia or (chronic or permanent) adj3 paralysis or sci or (spine or spinal) adj7 (diabetes or prediabetes or metabolic syndrome or (metabolism adj2 (profile or response or reflex or react or function or dysfunction or alter or impair) or hyperglycemia or (elevated or high or impair) adj3 glucose). mp. (2)
3. (paraplegia or quadriplegia or tetraplegia or hemiplegia or (chronic or permanent) adj3 paralysis or sci or (spine or spinal) adj7 (hypercholesterol or hyperlipid or hyperlipoprotein or syndrome x or metabolic x or metabolic syndrome or (elevate or high or impair) adj3 (blood pressure or cholesterol or triglyceride or lipid or LDL or HDL or lipoprotein). mp. (0)
4. (paraplegia or quadriplegia or tetraplegia or hemiplegia or (chronic or permanent) adj3 paralysis or sci or (spine or spinal) adj7 (hemodynamic or baroreflex or metaboreflex or ((circulation or vasoconstriction) adj3 (response or reflex or react or function or dysfunction or alter or impair). mp. [mp=title, text, subject heading word] (0)
5. (paraplegia or quadriplegia or tetraplegia or hemiplegia or (chronic or permanent) adj3 paralysis or sci or (spine or spinal) adj7 (hemodynamic or baroreflex or metaboreflex or ((circulation or vasoconstriction) adj3 injury) adj7 (obese or adipose or body fat or (abdominal adj2 fat) or body mass index or bmi or body composition or body measure). mp. [mp=title, text, subject heading word] (0)
6. (paraplegia or quadriplegia or tetraplegia or hemiplegia or (chronic or permanent) adj3 paralysis or sci or (spine or spinal) adj7 (hemodynamic or baroreflex or metaboreflex or circulation or vasoconstriction) adj5 (physiopathology or pathophysiology). mp. [mp=title, text, subject heading word] (0)
7. (paraplegia or quadriplegia or tetraplegia or hemiplegia or (chronic or permanent) adj3 paralysis or sci or (spine or spinal) adj7 (hemodynamic or baroreflex or metaboreflex or (circulation or vasoconstriction) adj7 (C-reactive protein$ or c-rp or crp or interleukin 6 or interleukin six or il-6 or tissue necrosis factor alpha or tissue necrosis factor a or tnf-alpha or tnf-a)). mp. (0)
8. (paraplegia or quadriplegia or tetraplegia or hemiplegia or (chronic or permanent) adj3 paralysis or sci or (spine or spinal) adj7 (hemodynamic or baroreflex or metaboreflex or ((circulation or vasoconstriction) adj7 (thrombosis or embolism or blood clot).mp. (1)
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (5)

PVA Known Authors - Cardiometabolic Disorders in Individuals with Spinal Cord Injury:

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to October Week 2 2015>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <October 20, 2015>

Search Strategy:

1. (spine or spinal) adj3 injury).mp. (49270)
2. exp Spinal Cord Injuries (40227)
3. exp Spinal Cord (84242)
4. 1 or 2 or 3 (135265)
5. paralysis/ or paraplegia/ or quadriplegia/ (36227)
6. (paralysis or paraplegia or hemiplegia or quadriplegia or tetraplegia). mp. (373231)
7. 5 or 6 (373231)
8. brenes g.au. (15)
9. dearwater s.au. (12)
10. bauman wa.au. (257)
11. nash ms.au. (118)
12. groah sl.au. (31)
13. gater d or gater dr .au. (58)
14. myers j.au. (975)
15. lieberman ja.au. (601)
16. sabharwal s.au. (144)
17. gorgey as.au. (43)
18. figoni s or figoni sf.au. (34)
19. davis gm.au. (207)
20. phillips e.au. (385)
21. weaver fm.au. (127)
22. spungen am.au. (121)
23. dyson-hudson t or dyson-hudson ta .au. (16)
24. wahman k.au. (9)
25. buchholz ac.au. (41)
26. noreau l.au. (88)
27. van der woude l.au. (15)
28. janssen tw.au. (75)
29. hopman mt.au. (219)
30. hicks al.au. (86)
31. glaser rm.au. (65)
32. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 (3563)
33. 4 and 7 and 32 (310)

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