Identification and Management of Cardiometabolic Risk after SCI

An Evidence-Based Clinical Practice Guideline
Paralyzed Veterans of America
Consortium for Spinal Cord Medicine

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Georgetown University, and the Uniformed University of the Health Sciences
Guideline Synthesis

- Panel invitations and commitment; 2 Panelists subsequently withdrew; 1 for time conflict, 1 for illness
- Search explication of 80 key words and 20 additional authors > 780 articles identified, 149 articles rated by the librarians.
- ‘Charge Meeting’ at PVA Headquarters (October 2016)
  - Established Writing and Review Deadlines; Generated and agreed upon the Guideline outline
  - Named 1st and 2nd writers for each Guideline section
- Preliminary Draft from 1st and 2nd writers was sent to all panelists for written comment and editing (End of January 2017); Writing assignments returned to Chair/Co-Chair for reconciliation
- Editing and reconciliation by Chair/Co-Chair – 5 versions (2nd week of February)
  - V.6 redistributed to all Panelists for comment
- 2nd (Reconciliation) meeting at PVA Headquarters (Late February 2017)
- Corrections from 2nd meeting incorporated (2nd week in March)
- V.7 literature grading and assessment of Panel agreement (late April, 2017)
  - ‘Grade Method’ incorporated in documents
- V.8 distributed to Consortium Reviewers (Early June, 2017)
- Thus far, received 27 Consortium Reviews and 2 Non-affiliated Expert Reviews
“The following Guideline is the first of the Consortium for Spinal Cord Medicine to address Cardiometabolic Disease (CMD) after spinal cord injury.

In doing so, it reports concern for all-cause cardiovascular diseases (CVD) and CVD-related risks as significant health hazards for persons with spinal cord injury (SCI), and, establishes a foundational standard for identification and management of cardiometabolic risks.”
Nomenclature for Rating of Evidence from 193 articles, and Strength of Panel Agreement (Grade Method)

**LEVELS OF SCIENTIFIC EVIDENCE**

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 of 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.


**CATEGORIES OF THE STRENGTH OF EVIDENCE ASSOCIATED WITH THE RECOMMENDATIONS**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>The guideline recommendation is supported by one or more level I studies</td>
</tr>
<tr>
<td>B</td>
<td>The guideline recommendation is supported by one or more level II studies</td>
</tr>
<tr>
<td>C</td>
<td>The guideline recommendation is supported by only one or more level III, IV, or V Studies</td>
</tr>
</tbody>
</table>

**LEVELS OF PANEL AGREEMENT WITH THE RECOMMENDATIONS**

<table>
<thead>
<tr>
<th>Level</th>
<th>Mean Agreement Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>1.0 to less than 2.33</td>
</tr>
<tr>
<td>Moderate</td>
<td>2.33 to less than 3.87</td>
</tr>
<tr>
<td>Strong</td>
<td>3.87 to 5.0</td>
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</table>
Cardiometabolic Disease

• A clustering of interrelated risk factors that promote the development of atherosclerotic vascular disease and type 2 diabetes mellitus.
• The syndrome is comprised of maladaptive cardiovascular, renal, metabolic, pro-thrombotic, and inflammatory pathologies, and has five component risks of:
  • obesity, insulin resistance, hypertension, and dyslipidemia (e.g., low high-density lipoprotein cholesterol and elevated triglycerides)
Cardiometabolic Risk Factors

- Traditional Component Risks
  - Age
  - Family History
  - Gender
  - Hypertension
  - Hypercholesterolemia
  - Type II Diabetes
  - Tobacco Use

- Cardiometabolic Syndrome
  - Abdominal Obesity
  - Insulin Resistance / Type II Diabetes
  - Hypertension
  - Hypertriglyceridemia
  - Low High-Density Lipoproteinemia

- Non-Traditional Component Risks
  - Genetics
  - Prothrombotic State
  - Proatherogenic State

- Physical deconditioning
- Nutritional deficiency
- Pro-inflammatory state
Organization of Recommendations

1. CMD and CMD Component Risks Accompanying SCI
   a. CMD
      1) Obesity
      2) Insulin Resistance
      3) Dyslipidemia (Low HDL and Elevated TG)
      4) Hypertension

2. Method for CMD Diagnosis, and CMD Risk Identification
   a. CMD
      1) Obesity
      2) Insulin Resistance
      3) Dyslipidemia (Low HDL and Elevated TG)
      4) Hypertension

<table>
<thead>
<tr>
<th>Authority</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHA (2004)</td>
<td>Three or more of:</td>
</tr>
<tr>
<td></td>
<td>Waist circumference:</td>
</tr>
<tr>
<td></td>
<td>• Men — greater than 40 inches (102 cm)</td>
</tr>
<tr>
<td></td>
<td>• Women — greater than 35 inches (88 cm)</td>
</tr>
<tr>
<td></td>
<td>Plasma triglycerides: ≥ 150 mg/dL (1.7 mmol/L)</td>
</tr>
<tr>
<td></td>
<td>Reduced HDL (&quot;good&quot;) cholesterol: Men — Less than 40</td>
</tr>
<tr>
<td></td>
<td>mg/dL (1.03 mmol/L)</td>
</tr>
<tr>
<td></td>
<td>Women — Less than 50 mg/dL (1.29 mmol/L)</td>
</tr>
<tr>
<td></td>
<td>Elevated blood pressure: ≥ 130/85 mm Hg or use of medication</td>
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<tr>
<td></td>
<td>for hypertension</td>
</tr>
<tr>
<td></td>
<td>Fasting glucose ≥100 mg/dL (5.6 mmol/L) or use of medication</td>
</tr>
<tr>
<td></td>
<td>for hyperglycemia</td>
</tr>
</tbody>
</table>
3. Management of CMD Risk Components After SCI, including Surveillance Intervals
   a. Lifestyle Intervention
      1) Nutrition
      2) Exercise
   b. Medication
   c. Surgery

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<tr>
<td></td>
<td>use of medication for hyperglycemia</td>
</tr>
</tbody>
</table>
Obesity: Panel Findings of Risk

- 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.
Insulin Resistance: Panel Findings of Risk

- 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.
Dyslipidemia: Panel Findings of Risk

• 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.
Hypertension: Panel Findings of Risk

- The prevalence of hypertension in people with SCI varies with the attributes of the population being studied, including injury level, severity, and etiology.
Panel Findings of Supplementary CMD Risks Accompanying SCI

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

• Nutrition
  • 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.

• Inflammation
  • CRP and other inflammatory biomarkers represent a unique subclinical risk component of CMD the SCI population.
  • The role for CRP and other inflammatory biomarkers in risk identification, development, and diagnosis of CMD and CMD risk components for the SCI population requires further exploration.
Recommendations: Based upon PVA Clinical Practice Guideline Orientation Manual (2014)

“The recommendations and suggestions are based on the available evidence and, where there is limited evidence, on panel experience and consensus, with an overall objective to improve the care of patients with spinal cord injury and to guide clinicians and policymakers.”

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, strength of the evidence, and level of panel agreement with the recommendations.

* Not a mandate!
1. Use the American Heart Association (AHA) definition, and constituent hazards of obesity, insulin resistance, dyslipidemia (low high-density lipoprotein cholesterol [HDL-C] and elevated Triglyceride [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 who are already discharged from rehabilitation, evaluate at the earliest opportunity.

   (Scientific evidence- V; Grade of recommendation- C, Level of Panel Recommendation - Strong)
3. Assess obesity beginning at discharge from rehabilitation:
   a. Where possible measuring 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)*

4. 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

5. 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)

6. Adopt ADA guidelines to diagnose diabetes and prediabetes based on either fasting plasma glucose (FPG), the 2-hour plasma glucose (2-h PG) value after a 75-g oral glucose tolerance test (OGTT), or A1C criteria.

(Scientific evidence- IV; Grade of recommendation- C, Level of Panel Recommendation - Strong)
Hypertension Recommendations

7. 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)

8. 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)

<table>
<thead>
<tr>
<th>Patient Subgroup</th>
<th>Target SBP (mm Hg)</th>
<th>Target DBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60 years</td>
<td>&lt;150</td>
<td>&lt;90</td>
</tr>
<tr>
<td>&lt; 60 years</td>
<td>&lt;140</td>
<td>&lt;90</td>
</tr>
<tr>
<td>&gt; 18 years with CKD</td>
<td>&lt;140</td>
<td>&lt;90</td>
</tr>
<tr>
<td>&gt; 18 years with diabetes</td>
<td>&lt;140</td>
<td>&lt;90</td>
</tr>
</tbody>
</table>

CKD = chronic kidney disease; DBP = diastolic blood pressure; SBP = systolic blood pressure

Dyslipidemia Recommendations

9. Surveillance in asymptomatic adults with SCI of fasting LDL (estimated using the Friedewald equation 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)

10. 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)
Table 2. Recommended schedule for surveillance and follow-up of cardiometabolic risk after SCI.

<table>
<thead>
<tr>
<th>Risk</th>
<th>Test</th>
<th>Patients</th>
<th>Initial</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMD</td>
<td>S+ risk components (see below)</td>
<td>All</td>
<td></td>
<td>See Individual Risk Components</td>
</tr>
<tr>
<td>Impaired Fasting Glucose, Pre-Diabetes and Diabetes</td>
<td>Fasting plasma glucose [FG], OGTT, or A1C</td>
<td>Asymptomatic adults with SCI</td>
<td>Screen adults with SCI for diabetes and prediabetes, and repeat testing at least every 3 years if tests are normal</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>Multi-compartment modeling or BMI</td>
<td>All</td>
<td></td>
<td>Annual testing and ongoing management. Institute lifestyle management, and if necessary, drug therapy (Table 4)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Fasting lipid panel preferred, but at minimum HDL-C and TG</td>
<td>All</td>
<td>At discharge from rehabilitation</td>
<td>Annual testing, or when evidence of elevated risk is identified. Measured at every routine visit (and at least annually). Elevated BP readings should be confirmed on a separate visit to diagnose hypertension. Repeat blood pressure measurements over time and measure blood pressure in both the supine and seated positions to account for postural influences and blood pressure variability due to autonomic instability.</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Blood Pressure</td>
<td>All</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifestyle Risk Factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suboptimal Nutrition</td>
<td>Maintenance of stable body fat mass or whole-body mass throughout the lifespan</td>
<td>All</td>
<td>Medically supervised nutrition plan beginning in rehabilitation, or as soon as possible</td>
<td>Continuous throughout the lifespan</td>
</tr>
<tr>
<td>Physical Deconditioning</td>
<td>Exercise testing if practical</td>
<td>All, insofar as feasible and practical</td>
<td>Recommendation s for therapeutic or recreational exercise initiated by the time of rehabilitation discharge</td>
<td>Annual assessment with continuous follow-up throughout the lifespan</td>
</tr>
</tbody>
</table>
Management of CMD Risk Components After SCI
Lifestyle Intervention: Nutrition

11. 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)

12. 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)
13. Individuals with SCI should participate in at least 150 minutes per week of 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 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 amounts and types of physical activity that are appropriate for their abilities.

(Scientific evidence- IV; Grade of recommendation- C, Level of Panel Recommendation - Strong)
14. 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)*

15. 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)*
In General...There is:

• A need for broadened surveillance and treatment of obesity starting early 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.

• 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.
Obesity Pharmacotherapies:
All ‘off-label’ and none tested for safety, tolerance, or effectiveness in persons with SCI

• Orlistat is a potent gastrointestinal lipase inhibitor that reduces dietary fat absorption by approximately 30%. Risks are for urgent diarrhea. The Panel feels that use of this agent in persons with SCI (i.e., a neurogenic bowel) is hazardous and poses unnecessary social risks.

• Phentermine/Topiramate is multitherapy pharmaceutical containing a low-dose of the centrally acting appetite suppressant phentermine and the antiepileptic agent 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. 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.
Obesity Pharmacotherapies

- Lorcaserin is a 5-hydroxytryptamine (5-HT2C) selective agonist that primarily acts on the hypothalamus to suppress appetite. 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 a 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. 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.
Obesity Pharmacotherapies: Summary

• In summary, none of the FDA-approved drugs for treating obesity are approved for use (i.e., on-label) for SCI.

• All have adverse effects that may substantially affect 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 to drug therapy, which 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.
16. 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)*

17. 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 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, 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. Consider referral to an endocrinologist.

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

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

19. 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

20. Apply evidence-based guidelines for treating hypertension in the general population to 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)

21. 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)
22. 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, a SCI specialist should provide preoperative, perioperative and postoperative consultative services to the surgical and anesthesia teams to alert them of unique risks associated with SCI.

   (Scientific evidence- V; Grade of recommendation- C, Level of Panel Recommendation - Strong)
Bariatric Surgery Warnings

- 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, spasticity.

- The odds ratio for venous thromboembolism in SCI after bariatric surgery has recently been determined as 5.71 (95% CI 1.36-24.02). Other potential complications associated with such surgeries include:
  - abdominal pain/cramping, dumping syndrome, beriberi, postoperative adhesions and loose stools have not been characterized or reported.
Table 4. Recommended lifestyle management and pharmacotherapy for persons with SCI.

<table>
<thead>
<tr>
<th>Cardiometabolic Risk</th>
<th>Goal</th>
<th>Primary Management: Lifestyle Intervention</th>
<th>Secondary Management: Pharmacotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMD Diagnosis</td>
<td>Reduce number of risk components to &lt; 3</td>
<td>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, fried foods and red meats; 2. Limit saturated fat to 5-6% of total caloric intake; and 3. Limit daily sodium intake to ≤ 2400 mg for individuals with hypertension.</td>
<td>None recommended</td>
</tr>
<tr>
<td>Overweight or Obese</td>
<td>Reduce body fat mass to achieve &lt; 22%, or a BMI &lt; 22 kg/m²</td>
<td>Encourage participation at least 150 minutes per week of moderate-intensity physical exercise according to ability beginning as soon as possible following acute spinal cord injury. The 150 minute per week guideline can be satisfied by sessions of 30-40 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.</td>
<td>Metformin (Glucophage) as the first line agent for treatment of HbA1c &gt;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.</td>
</tr>
<tr>
<td>Insulin Resistance, Type 2 Pre-Diabetes, or Type 2 Diabetes</td>
<td>Reduce FPG to ≤100 mg/dL and HbA1c &lt; 7%</td>
<td></td>
<td>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 nonblack population, and either a thiazide-type diuretic or CCB in the black population. Consider SCI-related factors when selecting an antihypertensive agent, such as the effect of thiazide diuretics on bladder management.</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Reduce TG to ≤ 135 mg/dL and increase HDL-C to ≥ 40 mg/dL (males) and ≥ 50 mg/dL (females)</td>
<td></td>
<td>As above</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Reduce BP to ≤ 140 mmHg and BP to &lt; 90 mmHg</td>
<td></td>
<td>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).</td>
</tr>
</tbody>
</table>
Recommendations for Future Research

1. In general, more 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 focusing 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. Guideline-supported interventions for the general population should be assessed in populations with SCI to determine safety and efficacy in this population given their unique physiology.
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.
Directions for Future Research (Continued)

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 risks based on age at injury, 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 if possible modified for the SCI population to forecast future risks for all-cause events and death.

10. Big data descriptions of CMD prevalence (for example, using electronic health records, Veteran’s Health Administration, private or public insurance data, etc.).
11. Randomized trials of screened/unscreened populations and controlled interventions 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 targeting 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. (i.e., Harris-Benedict-'like' equations)

15. Identification of population-specific pharmacotherapy, and related treatment benefits, risks, and all-cause burdens.

16. Imaging and phenotypic assessments to develop and optimize integrated risk markers and tools for early screening and detection of CMD.
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