

# Chapter 16: Hypertension, Dyslipidemias, Tobacco Use, and Obesity

## 16.1: HYPERTENSION

**16.1.1: We recommend measuring blood pressure at each clinic visit. (1C)**

**16.1.2: We suggest maintaining blood pressure at <130 mm Hg systolic and <80 mm Hg diastolic if  $\geq 18$  years of age, and <90<sup>th</sup> percentile for sex, age, and height if <18 years old. (2C)**

**16.1.3: To treat hypertension (Not Graded):**

- use any class of antihypertensive agent;
- monitor closely for adverse effects and drug–drug interactions; and
- when urine protein excretion  $\geq 1$  g/day for  $\geq 18$  years old and  $\geq 600$  mg/m<sup>2</sup>/24 h for <18 years old, consider an ACE-I or an ARB as first-line therapy.

**ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.**

## Background

Most guidelines for the general population define hypertension as persistent systolic blood pressure on at least 2 days  $\geq 140$  mm Hg and/or diastolic blood pressure  $\geq 90$  mm Hg if age  $\geq 18$  years, and  $\geq 95^{\text{th}}$  percentile for gender, age and height if age <18 years (Table 22). However, these same guidelines establish treatment goals for high-risk subpopulations, for example diabetes and CKD, that are generally systolic <130 mm Hg and/or diastolic <80 mm Hg for adults, and <90<sup>th</sup> percentile for gender, age and height for adolescents and children.

## Rationale

- In the general population, there is strong evidence that treatment of hypertension is effective in preventing CVD and in retarding the progression of CKD.
- In KTRs, the prevalence of hypertension is high enough to warrant screening.
- In KTRs, blood pressure is a risk factor for CVD and CAI.
- In KTRs, there is little reason to believe that the prevention and treatment of hypertension would not also prevent CVD and kidney allograft injury.

Observational studies and RCTs have conclusively shown that hypertension is an independent risk factor for CVD and CKD in the general population.

In addition, evidence from RCTs in the general population has conclusively shown that reducing blood pressure reduces the risk of CVD. These trials have shown benefit to reducing blood pressure to <140/90 mm Hg even in low-risk adult populations. Additional benefit may extend to high-risk populations, such as those with diabetes. RCTs in CKD have generally shown that blood pressure reduction reduces proteinuria and slows the rate of decline in kidney function.

Life expectancy is lower in KTRs than in the general population, and it is possible that the benefits and harm of hypertension treatment in KTRs are different than in the general population. However, the leading cause of death in KTRs is CVD, making it likely that treatments that reduce the risk of CVD in the general population will also be cost-effective in KTRs. Although adverse effects of pharmacological treatment of hypertension in KTRs are different and likely more common than in the general population, small RCTs and observational studies suggest that these adverse effects are generally not severe enough to reduce quality of life or increase mortality.

The incidence of hypertension in KTRs is 50–90% (435,542,543). Thus, even conservative estimates on the incidence of hypertension in KTRs suggest that hypertension is common enough to warrant close scrutiny in KTRs. Observational studies have shown that hypertension is an independent risk factor for CVD after kidney transplantation (Table 18) (430,544). There are also studies linking hypertension to poor graft function, although it is difficult to separate cause and effect relationships in these studies (545–547).

There are few data to suggest how often patients should be screened for hypertension after kidney transplantation. However, the high incidence of hypertension, the changing risk for hypertension and CVD in KTRs and the ease of obtaining blood pressure measurements are compelling arguments for measuring blood pressure at every clinic visit. Patients should be seated quietly for at least 5 min with feet on the floor and arm supported at heart level. An appropriately sized cuff with bladder encircling at least 80% of the arm should be used. At least two measurements should be made. Systolic blood pressure is the point at which the first of two or more sounds is heard (phase 1),

**Table 22:** Guideline definitions of hypertension

| Guideline                   | Hypertension definition                   | Treatment goals (mm Hg)                   |                                                                                 |
|-----------------------------|-------------------------------------------|-------------------------------------------|---------------------------------------------------------------------------------|
|                             |                                           | All                                       | In sub-populations                                                              |
| JNC 7 2003 (536)            | ≥140/90                                   | <140/90                                   | <130/80 in diabetes and CKD                                                     |
| WHO ISH 2003 (537)          | ≥140/90                                   | <140/90                                   | <130/80 in diabetes                                                             |
| KDOQI 2004 (538)            |                                           | –                                         | <130/80 in KTRs                                                                 |
| NHBPEWG Children 2004 (539) | ≥95 <sup>th</sup> percentile <sup>a</sup> | <95 <sup>th</sup> percentile <sup>a</sup> | <90 <sup>th</sup> percentile <sup>a</sup> in concurrent conditions <sup>b</sup> |
| ESH ESC 2007 (540)          | ≥140/90                                   | <140/90                                   | <130/80 in diabetes and high risk <sup>c</sup>                                  |
| USPSTF 2007 (541)           | ≥140/90                                   | See JNC 7 <sup>d</sup>                    | See JNC 7 <sup>d</sup>                                                          |

CKD, chronic kidney disease; ESC, European Society of Cardiology; ESH, European Society of Hypertension; ISH, International Society for Hypertension; JNC, Joint National Committee; KDOQI, Kidney Disease Outcomes Quality Initiative; KTRs, kidney transplant recipients; NHBPEWG, National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents; USPSTF, United States Preventative Services Task Force; WHO, World Health Organization.

<sup>a</sup>For gender, age and height on three occasions.

<sup>b</sup>Concurrent conditions are CKD, diabetes and hypertensive target-organ damage (539).

<sup>c</sup>High risk includes patients with stroke, myocardial infarction, renal dysfunction and proteinuria.

<sup>d</sup>Recommends screening age >18 years and uses JNC 7 treatment thresholds (536).

and diastolic blood pressure is the point before the disappearance of sounds (phase 5). Patients should be provided with their specific blood pressure readings and goals (536).

Ambulatory blood pressure monitoring is warranted for the evaluation of possible 'white coat hypertension,' episodic hypertension, assessing apparent drug resistance, hypotensive symptoms with blood pressure treatment and autonomic dysfunction (536). Ambulatory blood pressure readings are lower than office blood pressure readings, with daytime values being higher than values during sleep (Table 23) (536).

Self-measured blood pressure is also useful in assessing treatment of hypertension and improving adherence to treatment (536). Home measurement devices should be checked regularly for accuracy.

It is unlikely that there will be RCTs in KTRs to determine whether blood pressure lowering reduces CVD events, or prolongs patient or graft survival. However, observational studies have reported that hypertension is associated with both CVD events and graft survival (Table 18). Guidelines from the general population recommend targeting <140/90 mm Hg for all patients, even low-risk patients. However, these same guidelines recommend targeting <130/80 mm Hg for high-risk patients, such as patients with diabetes and CKD (536,538). There are indeed RCT data justifying this lower target in these populations. Although many transplant patients have diabetes and many have reduced GFR, whether benefits outweigh risks of targeting <130/80 mm Hg is unclear.

Causes of posttransplant hypertension include CNI use, corticosteroids, kidney allograft dysfunction, allograft vascular compromise (from within the allograft itself, from within the allograft artery and its anastomosis and from

within arteries immediately proximal to the allograft artery anastomosis) (548–553), as well as factors related to the presence of the native kidneys (554–556). Treatment should include adjusting CNI dose, administering antihypertensive medications and managing other CVD risk factors. A number of small randomized trials have demonstrated the efficacy and safety of lowering blood pressure with most classes of antihypertensive medications. However, there is insufficient evidence to recommend any class of antihypertensive agents as preferred for long-term therapy for reducing CVD or improving long-term graft survival.

The choice of initial antihypertensive agent may be determined by the presence of one or more common posttransplant complications that may be made better or worse by specific antihypertensive agents (Table 24). Urine protein excretion ≥1 g per 24 h if age ≥18 years (and ≥600 mg/m<sup>2</sup> per 24 h if age <18 years) is a threshold at which blood pressure lowering trials have shown efficacy in reducing the progression of kidney disease in nontransplant patients (538). To date, there are no RCTs showing that reducing urinary protein in KTRs preserves kidney allograft function.

In general, no antihypertensive agent is contraindicated in KTRs. Data from nontransplant patients with CKD suggest that ACE-Is and ARBs may have beneficial effects on

**Table 23:** Adult blood pressure thresholds for defining hypertension

| Method of measurement | Threshold (mm Hg) |
|-----------------------|-------------------|
| Office or clinic      | 140/90            |
| 24-h average          | 125–130/80        |
| Daytime               | 130–135/85        |
| Night-time            | 120/70            |
| Home (daytime)        | 130–135/85        |

Modified with permission (540).

**Table 24:** Advantages and disadvantages of major antihypertensive agent classes in KTRs

| Agent class                                          | Advantages (additional indications that are common in KTRs)                                                                                         | Disadvantages (adverse effects that are common in KTRs)                                 |
|------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| Thiazide diuretics                                   | CHF with systolic dysfunction<br>High CAD risk<br>Recurrent stroke prevention<br>Hyperkalemia<br>Edema                                              | Hypomagnesemia<br>Hyperuricemia<br>Hyponatremia<br>Dyslipidemias<br>Glucose intolerance |
| Aldosterone antagonists                              | CHF with systolic dysfunction<br>Post MI                                                                                                            | Hyperkalemia                                                                            |
| Beta-blockers                                        | CHF with systolic dysfunction <sup>a</sup><br>Chronic stable angina<br>Post MI<br>High CAD risk<br>Supraventricular tachycardia                     | Hyperkalemia<br>Dyslipidemias<br>Glucose intolerance                                    |
| Angiotensin-converting enzyme inhibitor <sup>c</sup> | CHF with systolic dysfunction<br>Post MI<br>High CAD risk<br>Recurrent stroke prevention<br>Reduce proteinuria<br>Polycythemia                      | Hyperkalemia<br>Anemia                                                                  |
| Calcium-channel blockers                             | Chronic stable angina<br>High CAD risk<br>Supraventricular tachycardia<br>Increased CNI levels (allowing a reduction in dose and cost) <sup>b</sup> | Edema<br>Increased CNI levels <sup>b</sup><br>Reduced kidney function                   |

ARB, angiotensin II receptor blocker; CAD, coronary artery disease; CHF, congestive heart failure; CNI, calcineurin inhibitor; KTRs, kidney transplant recipients; MI, myocardial infarction.

<sup>a</sup>Carvediol, bisoprolol, metoprolol succinate.

<sup>b</sup>Nondihydropyridine calcium blockers.

<sup>c</sup>ARBs may have similar effects as ACE-Is and may be used in patients who do not tolerate ACE-Is.

the progression of diabetic and nondiabetic CKD, particularly in patients with proteinuria (538). However, RCTs in KTRs have not had sufficient statistical power to determine whether ACE-I or ARB therapy improves patient or graft survival (557). On the other hand, ACE-Is and ARBs may be associated with an increased risk of hyperkalemia and anemia in KTRs (557–560). Hypertensive KTRs with ischemic heart disease and/or CHF may benefit from ACE-Is, ARBs and/or beta-blockers (561). Diuretics may be effective in treating hypertension in KTRs, since hypertension in CNI-treated KTRs may be sodium dependent (562).

Many patients will require combination therapy to control blood pressure. Most combinations should include a thiazide diuretic, unless it is contraindicated. Recent studies suggest that thiazides may be more effective than previously thought in patients with reduced kidney function (563–565). When hypertension is difficult to control, especially when it is associated with otherwise unexplained kidney allograft dysfunction, screening for allograft vascular compromise, within or proximal to the allograft artery, should be considered. This usually requires imaging of the allograft vasculature using either an angiogram, computerized tomographic angiography or magnetic resonance imaging. When hypertension is difficult to control,

and there are no reversible causes, bilateral native kidney nephrectomies may be considered, especially in a KTR <40 years old.

## Research Recommendations

Randomized controlled trials are needed to determine:

- the optimal blood pressure treatment target in KTRs;
- the effect of reducing proteinuria on progression of CKD in KTRs;
- the effects of ACE-Is/ARBs on patient survival and graft survival.

### 16.2: DYSLIPIDEMIAS

**(These recommendations are based on KDOQI Dyslipidemia Guidelines and are thus *Not Graded*)**

- 16.2.1: Measure a complete lipid profile in all adult ( $\geq 18$  years old) and adolescent (puberty to 18 years old) KTRs (based on KDOQI Dyslipidemia Recommendation 1):**
- 2–3 months after transplantation;

- 2–3 months after a change in treatment or other conditions known to cause dyslipidemias;
  - at least annually, thereafter.
- 16.2.2: Evaluate KTRs with dyslipidemias for secondary causes (based on KDOQI Dyslipidemia Recommendation 3)**
- 16.2.2.1: For KTRs with fasting triglycerides  $\geq 500$  mg/dL ( $\geq 5.65$  mmol/L) that cannot be corrected by removing an underlying cause, treat with:**
- **Adults: therapeutic lifestyle changes and a triglyceride-lowering agent (based on KDOQI Recommendation 4.1);**
  - **Adolescents: therapeutic lifestyle changes (based on KDOQI Recommendation 5.1).**
- 16.2.2.2: For KTRs with elevated LDL-C:**
- **Adults: If LDL-C  $\geq 100$  mg/dL ( $\geq 2.59$  mmol/L), treat to reduce LDL-C to  $< 100$  mg/dL ( $< 2.59$  mmol/L) (based on KDOQI Guideline 4.2);**
  - **Adolescents: If LDL-C  $\geq 130$  mg/dL ( $\geq 3.36$  mmol/L), treat to reduce LDL-C to  $< 130$  mg/dL ( $< 3.36$  mmol/L) (based on KDOQI Guideline 5.2).**
- 16.2.2.3: For KTRs with normal LDL-C, elevated triglycerides and elevated non-HDL-C:**
- **Adults: If LDL-C  $< 100$  mg/dL ( $< 2.59$  mmol/L), fasting triglycerides  $\geq 200$  mg/dL ( $\geq 2.26$  mmol/L), and non-HDL-C  $\geq 130$  mg/dL ( $\geq 3.36$  mmol/L), treat to reduce non-HDL-C to  $< 130$  mg/dL ( $< 3.36$  mmol/L) (based on KDOQI Guideline 4.3);**
  - **Adolescents: If LDL-C  $< 130$  mg/dL ( $< 3.36$  mmol/L), fasting triglycerides  $\geq 200$  mg/dL ( $\geq 2.26$  mmol/L), and non-HDL-C  $\geq 160$  mg/dL ( $\geq 4.14$  mmol/L), treat to reduce non-HDL-C to  $< 160$  mg/dL ( $< 4.14$  mmol/L) (based on KDOQI Guideline 5.3).**

**HDL-C, high-density lipoprotein cholesterol; KDOQI, Kidney Disease Outcomes Quality Initiative; KTRs, kid-**

**ney transplant recipients; LDL-C, low-density lipoprotein cholesterol.**

## Background

Dyslipidemias are abnormalities in circulating lipoproteins that are associated with an increased risk of CVD. The Work Group did not perform systematic reviews of the evidence for management of dyslipidemias in KTRs since this was performed recently for the KDOQI Dyslipidemia Guidelines. Rather, the recommendations of the Work Group are based on those of the KDOQI Dyslipidemia Guidelines for the management of dyslipidemia in CKD (566). The Work Group searched for, but did not find, large RCTs for dyslipidemia management in KTRs published since the publication of the KDOQI Dyslipidemia Guidelines. In addition, the Work Group searched for, but did not find, new guidelines for the management of dyslipidemia in the general population. Therefore, the Work Group concluded that there was little new evidence to require modification of the KDOQI Dyslipidemia Guidelines at this time. However, the Work Group amended the original guideline statements to apply to the KTRs.

## Rationale

- In the general population, there is strong evidence that reducing LDL-C decreases the risk for CVD events.
- In KTRs, there is little reason to believe that reducing LDL-C would not be safe and effective in reducing CVD events.
- In KTRs, the prevalence of dyslipidemia is high enough to warrant screening and intervention.
- In KTRs, there is moderate evidence that dyslipidemias contribute to CVD and that treatment of increased LDL-C with a statin may reduce CVD events.

A large number of RCTs in the general population have demonstrated that lowering LDL-C reduces CVD events and mortality. There is less evidence that treating other lipoprotein abnormalities, such as increased triglycerides or reduced HDL-C is effective. Guidelines generally recommend treating patients based on the level of LDL-C and the level of risk for CVD events.

Although there are drug–drug interactions that must be monitored in KTRs, the use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors ('statins') is generally safe and effective in lowering LDL-C, if appropriate dose modification is made for patients treated with CNIs. The use of other lipid-lowering therapies are less certain, but potentially beneficial in KTRs.

The incidence and prevalence of dyslipidemia is high in KTRs, in large part due to the fact that immunosuppressive

agents cause or contribute to dyslipidemias. Agents implicated in causing dyslipidemias include corticosteroids, CsA and mTORi. The overall prevalence of dyslipidemia during the first year after transplantation is >50%, although the prevalence is greatly influenced by the type of immunosuppression used and the presence of other factors, such as proteinuria, acute rejection and graft dysfunction. In any case, this high prevalence of dyslipidemia justifies screening and monitoring.

Observational studies suggest that hypercholesterolemia and increased LDL-C are independently associated with CVD events in KTRs. A RCT found that treatment of LDL-C with fluvastatin did not significantly reduce the primary end point (major adverse cardiac events) (567). However, important secondary end points, including mortality, were reduced by fluvastatin, and long-term follow-up suggested that major adverse cardiac events were also reduced (568). Thus, this study generally confirmed evidence from observational studies in KTRs, and RCTs in the general population, which indicate that increased LDL-C causes CVD, and treatment of LDL-C with a statin reduces the risk of CVD.

Although many measurements of lipoproteins can be linked to CVD events (e.g. apolipoprotein B, lipoprotein (a), etc.), the preponderance of evidence suggests that elevations in LDL-C are most closely associated with CVD. As a result, most guidelines target the screening and treatment of LDL-C. The measurement of LDL-C, or its estimation with the Friedewald formula, is reliable and generally available in most major laboratories around the world. The calculation of LDL-C requires a fasting lipid panel with total cholesterol, HDL-C and triglycerides. Directly measured LDL-C changes little with fasting or nonfasting, but direct measurement is less readily available.

Treating an underlying cause of dyslipidemia may improve the lipid profile. Although there are few data in KTRs, it is reasonable to expect that reducing or eliminating nephrotic-range proteinuria may improve the lipid profile. Similarly, treating poorly controlled diabetes may improve abnormal plasma lipids. Rarely, severe hypothyroidism may alter plasma lipoproteins. RCTs have shown that corticosteroids, CsA and especially mTORi can cause dyslipidemias in KTRs. In some cases, severe dyslipidemia may require modification of immunosuppressive medications.

The National Cholesterol Education Program Guidelines (569) and the KDOQI Guidelines on Dyslipidemia in KTRs (566) recommend first treating severe hypertriglyceridemia to avert the risk for pancreatitis. Very high levels of triglycerides (usually in the thousands) generally indicate elevations in chylomicrons. There is an association between severe hypertriglyceridemia and pancreatitis, prompting the recommendation to treat severe hypertriglyceridemia as the first priority. How often severe hypertriglyceridemia causes pancreatitis in KTRs is unknown.

If severe hypertriglyceridemia is not present, then LDL-C becomes the therapeutic target. In the KDOQI Dyslipidemia Guidelines, all adult KTRs are at high risk for ischemic heart disease, and therefore should be treated to maintain LDL-C <100 mg/dL (2.59 mmol/L) (566). The drug of first choice for reducing LDL-C is a statin. Doses of statins usually need to be reduced by approximately 50% in patients treated with CsA, and probably also in patients treated with tacrolimus (although fewer data are available).

The relatively small number of patients who have normal or low LDL-C, increased triglycerides and high non-HDL-C likely have high levels of atherogenic lipoprotein remnants. Treatment for these patients should be similar to treatment for patients with high LDL-C (566).

For adolescents, the KDOQI Dyslipidemia Guidelines increased the LDL-C target goal to reflect both the uncertainty of dyslipidemia treatment in adolescents, and possible the increased risk. The US Preventive Services Task Force (USPSTF) was unable to determine the balance between potential benefits and harm of screening children and adolescents for dyslipidemia (570). The National Cholesterol Education Program Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents recommended selective screening for children and adolescents with a family history of premature coronary heart disease or at least one parent with a high total cholesterol level (571).

### 16.3: TOBACCO USE

**16.3.1: Screen and counsel all KTRs, including adolescents and children, for tobacco use, and record the results in the medical record. (Not Graded)**

- Screen during initial transplant hospitalization.
- Screen at least annually, thereafter.

**16.3.2: Offer treatment to all patients who use tobacco. (Not Graded)**

**KTRs, kidney transplant recipients.**

### Background

Tobacco use includes the inhalation or ingestion of any tobacco product, including: the inhalation of tobacco smoke from cigarettes, cigars, water pipes or other devices; the nasal absorption of tobacco from snuff and the oral absorption and ingestion of tobacco from chewing.

## Rationale

- In the general population, there is strong evidence that tobacco use causes CVD, cancer, chronic lung disease and premature death.
- In the general population, there is strong evidence that screening, prevention and treatment measures are effective in adults. The effectiveness of clinician counseling of children and adolescents is uncertain.
- In KTRs, there is no reason to believe that the approach to prevention and treatment of tobacco use should be different than in the general population.
- In KTRs, cigarette smoking is associated with CVD and cancer.
- In KTRs, the prevalence of tobacco use is high enough to warrant intervention.

Evidence-based guidelines for the general population have concluded that there is strong evidence that tobacco use causes CVD, cancer and chronic lung disease (572–578). Although most studies have focused on cigarette smoking, there is evidence that any tobacco use is harmful (579). Evidence-based guidelines for the general population have also concluded that screening patients for tobacco use and implementing prevention and treatment measures are effective, at least in the short term, in improving the likelihood of abstinence in adults. However, there are few studies from the general population showing that interventions are effective for more than 1 year. There is also insufficient evidence that interventions are effective in children and adolescents.

A large number of observational studies have reported higher rates of CVD and mortality for cigarette smokers in the general population. In addition, there have been a large number of RCTs showing that different smoking cessation interventions are effective in increasing the number of patients who quit smoking (580–582). Recently, RCTs have also shown that smoking cessation interventions reduce mortality in the general population (583,584).

In KTRs, there is no reason to believe that the prevention and treatment of tobacco use would be different from that in the general population. In particular, there are no interac-

tions between pharmacotherapies for aiding in tobacco abstinence and immunosuppressive agents that would prevent the use of either in KTRs (Table 25).

Cigarette smoking at the time of kidney transplantation has been found to be an independent risk factor for patient survival, graft survival, ischemic heart disease, cerebral vascular disease, PVD and CHF (Table 18) (438,439,442,443,586,587). Smoking has also been found to be associated with posttransplant malignancies (588).

The prevalence of cigarette smoking at the time of transplantation varies between 25% and 50% (438, 439,586,588). The prevalence of smoking varies from country to country, likely due to differences in the prevalence of smoking in the general populations of those countries. However, even in countries where the prevalence is relatively low, it is high enough to warrant interventions.

Screening (and counseling) adults for tobacco use is recommended for the general population (572–576). Guidelines in the general population have cited a lack of evidence that screening adolescents and children is effective, although there is likely little harm in including children and adolescents (573). Screening patients includes asking them about their tobacco use history (including start and stop dates), amounts and types of tobacco used and prior interventions. Patients may not admit that they use tobacco, and nicotine levels have been used to identify smokers among KTRs (589). However, there is insufficient evidence for or against the use of laboratory testing to detect tobacco use in KTRs or in the general population.

There is no evidence to suggest when and how often to screen for tobacco use in KTRs. However, there are studies in the general population that indicate screening and intervention during hospitalization is more effective than usual care (575). Therefore, we recommend screening and intervention for patients during the initial hospitalization for kidney transplantation. There is no evidence to suggest the optimal interval after hospitalization for screening and intervention. However, given that initial screening may not be effective, follow-up screening would seem to be prudent. In addition, given the fact that at least some patients who do not use tobacco may begin to use tobacco at some time after transplantation, periodic screening is indicated.

**Table 25:** Pharmacological therapies for cigarette smoking cessation in KTRs

| Class                                                | Drug                                                  | Special considerations                                                                                                  |
|------------------------------------------------------|-------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|
| Nicotine replacement                                 | Nicotine gum, inhaler, nasal spray, lozenge and patch | May use in combinations with other nicotine and non-nicotine replacement agents                                         |
| Antidepressant                                       | Bupropion SR                                          | Monitor CsA blood levels and increase CsA dose as needed (585)                                                          |
| $\alpha_4\beta_2$ nicotinic receptor partial agonist | Varenicline                                           | Warn patients and monitor for serious neuropsychiatric symptoms including depression and suicidal ideation <sup>a</sup> |

<sup>a</sup>[www.fda.gov/Cder/Drug/infopage/varenicline/default.htm](http://www.fda.gov/Cder/Drug/infopage/varenicline/default.htm); last accessed June 21, 2008

The Work Group determined that annual screening is a reasonable minimum frequency.

Self-help is not adequate for smoking cessation. Both counseling and pharmacotherapy are effective, either alone or in combination. In general, the effectiveness of counseling is proportional to the amount of time spent counseling; however, even counseling for 3 min or less is effective (573). The '5 As' of counseling include: (i) ask about tobacco use, (ii) advise to quit through clear and personalized messages, (iii) assess willingness to quit, (iv) assist quitting and (v) arrange follow-up and support (573).

A number of different pharmacological therapies are effective in increasing the rate of smoking abstinence. There are five nicotine replacement aids and two other medications that have been shown to be effective in RCTs in the general population (Table 25) (580–582). These agents can and should be used in combination.

## Research Recommendations

- Randomized controlled trials are needed to determine the optimal approach(es) for reducing tobacco use in KTRs.

### 16.4: OBESITY

#### 16.4.1: Assess obesity at each visit. (Not Graded)

- Measure height and weight at each visit, in adults and children.
- Calculate BMI at each visit.
- Measure waist circumference when weight and physical appearance suggest obesity, but BMI is  $<35 \text{ kg/m}^2$ .

#### 16.4.2: Offer a weight-reduction program to all obese KTRs. (Not Graded)

**BMI, body mass index; KTRs, kidney transplant recipients.**

## Background

Obesity in adults is defined, as it is in major guidelines for the general population, as body mass index (BMI)  $\geq 30 \text{ kg/m}^2$  (Table 26). Because some individuals may have BMI  $\geq 30 \text{ kg/m}^2$  that is not due to excess body fat, it is recommended that the definition of obesity in adults include waist circumference  $\geq 102 \text{ cm}$  ( $\geq 40 \text{ in.}$ ) in men and  $\geq 88 \text{ cm}$  ( $\geq 35 \text{ in.}$ ) in women.

Body mass index can be calculated either as weight in kilograms divided by height in meters squared, or as weight in pounds divided by height in inches squared multiplied by 703 (both methods yielding units  $\text{kg/m}^2$ ).

**Table 26:** Definition and classification of obesity in adults

| Obesity class            | BMI ( $\text{kg/m}^2$ ) | Disease risk <sup>a</sup> |
|--------------------------|-------------------------|---------------------------|
| Underweight              | $<18.5$                 | –                         |
| Normal                   | 18.5–24.9               | –                         |
| Overweight               | 25.0–29.9               | Increased                 |
| Obesity, class 1         | 30.0–34.9               | High                      |
| Obesity, class 2         | 35.0–39.9               | Very high                 |
| Extreme obesity, class 3 | $\geq 40$               | Extremely high            |

BMI, body mass index.

<sup>a</sup>Disease risk is higher for people with large waist circumferences (men  $>102 \text{ cm}$  ( $>40 \text{ in.}$ ); women  $>88 \text{ cm}$  ( $>35 \text{ in.}$ )); risk for type 2 diabetes, hypertension and CVD.

Modified with permission (590).

In children, obesity is generally defined as BMI above the 95<sup>th</sup> percentile for age and sex. However, this definition is largely based on data from the US Caucasian population, and may be less applicable to other populations. The CDC and the American Academy of Pediatrics recommend the use of BMI to screen for overweight in children beginning at 2 years old ([www.cdc.gov/nccdphp/dnpa/bmi/childrens\\_BMI/about\\_childrens\\_BMI.htm](http://www.cdc.gov/nccdphp/dnpa/bmi/childrens_BMI/about_childrens_BMI.htm); last accessed March 30, 2009). For children, BMI is used to screen for overweight, at risk of overweight or underweight. However, BMI is not a diagnostic tool in children. For example, a child may have a high BMI for age and sex, but to determine if excess fat is a problem, a health-care provider would need to perform further assessments. These assessments might include skinfold thickness measurements, evaluations of diet, physical activity, family history and other appropriate health screenings.

The USPSTF found 'fair evidence' that BMI is a reasonable measure for identifying children and adolescents who are overweight, or at risk for becoming overweight, and that overweight children and adolescents are at increased risk for becoming obese adults. Therefore, BMI thresholds should be used to define overweight based on percentiles of the general population for age and sex (Table 27) (591).

**Table 27:** Definition and classification of obesity for children and adolescents 6 years of age and older

| Obesity risk                 | BMI ( $\text{kg/m}^2$ ) <sup>a</sup> | Risk                         |
|------------------------------|--------------------------------------|------------------------------|
| At risk for being overweight | 85–94 percentile                     | Becoming overweight          |
| Overweight                   | $\geq 95$ percentile                 | Being overweight as an adult |

BMI, body mass index.

<sup>a</sup>BMI calculated either as weight in kilograms divided by height in meters squared, or weight in pounds divided by height in inches squared multiplied by 703. Percentile for age and sex.

Modified with permission (591).

## Rationale

- In the general population, there is strong evidence that obesity is a risk factor for CVD events and mortality in adults.
- In the general population, there are few studies examining the effects of obesity treatment on CVD events or mortality, but there is evidence that the benefits of treating obesity on intermediate outcomes for CVD outweigh harm in adults.
- In KTRs, obesity is associated with CVD events and mortality.
- In KTRs, there is little reason to believe that weight reduction measures are not equally effective as in the general population; however, there is some reason to believe that pharmacological and surgical management of obesity may be more likely to cause harm than in the general population.

Observational studies in the general population have shown that obesity is an independent risk factor for CVD (592). Obesity is also associated with a number of risk factors for CVD, including hypertension, dyslipidemias and diabetes (590).

A number of RCTs in the general population have shown that diet may cause modest weight reduction, at least over a period of 12 months. Pharmacological interventions are more effective in weight loss than diet alone, but are associated with more adverse effects. Bariatric surgery is effective, and may improve health outcomes. Guidelines in the general population generally recommend screening and treatment of obesity ([www.cdc.gov/healthyweight/assessing/bmi/childrens\\_BMI/about\\_childrens\\_BMI.html](http://www.cdc.gov/healthyweight/assessing/bmi/childrens_BMI/about_childrens_BMI.html); last accessed July 27, 2009) (591,593–597).

Observational studies in adult KTRs have reported an association between obesity and mortality, CVD mortality and CHF (Table 18).

Counseling standard weight reduction diets, as recommended in guidelines in the general population, is unlikely to cause harm in KTRs. The effects of pharmacological management of obesity in KTRs are largely unexplored. Anecdotal evidence suggests that bariatric surgery can be performed safely in KTRs and results in weight loss, at least over a relatively short duration of follow-up (598–600).

Small, uncontrolled trials in KTRs suggest that diet and other behavior modifications are safe and help reduce weight over the short term (601,602). There is no evidence that any one diet is more effective than any other. A reasonable goal is to create a caloric deficit of 500–1000 kcal/day. Diets of 1000–1200 kcal/day for women and 1200–1500

kcal/day for men can be effective. Increased physical activity may help to sustain weight reduction and reduce CVD risk independent of weight reduction. Exercise may also be beneficial, although a small RCT in KTRs failed to show that counseling to encourage exercise reduced weight or CVD risk factors at 1 year (603). Nevertheless, exercise capacity increased in this study, and there was no harm associated with exercise.

A large number of RCTs have examined pharmacologic interventions for weight loss in the general population. These trials have shown modest weight reduction from medications vs. placebo at 12 months (604). There are few long-term studies, and even fewer studies that have examined health outcomes. In a 4-year RCT, 52% completed treatment with orlistat while 34% completed treatment with placebo. Mean weight loss was greater with orlistat (–5.8 kg) vs. placebo (–3.0 kg,  $p < 0.001$ ). The cumulative incidence of diabetes was 6.2% with orlistat vs. 9.0% with placebo ( $p = 0.0032$ ). In a RCT, comparing the cannabinoid receptor antagonist rimonabant with placebo in 839 patients, rimonabant failed to reduce the primary end point, change in atheroma volume on coronary intravascular ultrasound (605). Of concern are reports of psychiatric adverse effects from rimonabant (606). Altogether, it remains unclear whether the benefits outweigh harm of pharmacological management of obesity in the general population.

Pharmacological treatment of obesity has not been adequately studied in KTRs. Adverse effects of available agents limit their usefulness in the general population, and are likely to have an even greater potential for adverse effects in KTRs. Orlistat may interfere with the absorption of fat-soluble vitamins, and there have been case reports of an interaction between orlistat and CsA, resulting in lower CsA levels (607–609). Studies in the general population have shown that sibutamine can cause weight loss, but adverse effects are common and include increased blood pressure and heart rate (604). There have been no studies of sibutamine in KTRs.

There have been no RCTs examining the long-term effects of bariatric surgery on health outcomes in the general population. Nevertheless, bariatric surgery appears to be more effective than diet in causing weight reduction (610,611). In the largest case-control study to date, gastric bypass, vertical banded gastroplasty or gastric banding caused, respectively, –25%, –16% and –14% weight losses from baseline to 10 years (612). Importantly, there were 129 deaths in the control group and 101 deaths in the surgery group ( $p = 0.04$ ). The most common cause of death in this study was myocardial infarction (612). In another large observational study, all-cause mortality ( $p < 0.0001$ ), deaths from diabetes ( $p = 0.0005$ ) and deaths from coronary artery disease (CAD) ( $p = 0.006$ ) were lower among 7925 patients who had undergone bariatric surgery compared to 7925 matched controls (613). Thus, it appears that bariatric



**Table 28:** National Heart Lung Blood Institute weight-loss treatment guidelines<sup>a</sup>

| Treatment             | BMI (kg/m <sup>2</sup> ) |                                         |                                         |                                         |                                         |
|-----------------------|--------------------------|-----------------------------------------|-----------------------------------------|-----------------------------------------|-----------------------------------------|
|                       | 25–26.9                  | 27–29.9                                 | 30–34.9                                 | 35–39.9                                 | ≥40                                     |
| Behavior modification | Yes                      | Yes                                     | Yes                                     | Yes                                     | Yes                                     |
| Pharmacotherapy       |                          | If there are comorbidities <sup>b</sup> | Yes                                     | Yes                                     | Yes                                     |
| Bariatric surgery     |                          |                                         | If there are comorbidities <sup>c</sup> | If there are comorbidities <sup>c</sup> | If there are comorbidities <sup>c</sup> |

BMI, body mass index.

a. Modified with permission (590).

b. Comorbidities considered important enough to warrant pharmacotherapy are: established coronary heart disease, other atherosclerotic diseases, type 2 diabetes, sleep apnea, hypertension, cigarette smoking, high LDL-C, low HDL-C, impaired fasting glucose, family history of early CVD, and age (male ≥45 years, female ≥55 years).

c. Comorbidities considered important enough to warrant surgery are: established coronary heart disease, other atherosclerotic diseases, type 2 diabetes, and sleep apnea.

surgery can produce sustained weight reduction and improve health outcomes.

Guidelines in the general population recommend weight loss surgery in patients with severe obesity, that is BMI ≥40 kg/m<sup>2</sup> or ≥35 kg/m<sup>2</sup> with comorbid conditions. Bariatric surgery may include gastric banding or gastric bypass (Roux-en-Y). Uncontrolled studies suggest that bariatric surgery may be performed safely in selected KTRs (598–600). However, the incidence of complications may also be greater in KTRs (614).

Guidelines in the general population recommend tailoring treatment to the severity of obesity and its comorbidities (Table 28).

Childhood obesity in the general population is associated with a higher prevalence of CVD risk factors, such as

dyslipidemias, hypertension and diabetes. However, CVD events may take decades to develop. Few studies have examined the safety and efficacy of weight reduction in children or adolescents. The USPSTF concluded that evidence was insufficient to recommend for or against routine screening for obesity in children and adolescents as a means to prevent adverse health outcomes. There are likewise few studies on the treatment of obesity in children and adolescent KTRs; therefore, there is no basis for a different recommendation than for the general population.

## Research Recommendations

- Additional research is needed to determine the effect of bariatric surgery on outcomes in KTRs.