FSG 600-01
AIRCREW CARDIOVASCULAR RISK SCREENING

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REFERENCES:

A. CFHS P&G 4000-16 Periodic Health Examination - Aircrew
B. CFAO 34-44 - Periodic Health Examination and Medical Administration - Aircrew
C. FSG 1900-01-Medications and Aircrew

D. Gray G, Davenport ED, Bron D et al. The challenge of asymptomatic heart disease in aircrew: detecting plaque before the accident. HEART 2019 Suppl 1, ps17-24

E. Pearson GJ, Thanassoulis G, Anderson TJ et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults. CJC 2021 37(8); 1121-1150. DOI: https://doi.org/10.1016/j.cjca.2021.03.016

RECORD OF AMENDMENTS:

Date (DD/MMM/YY)	Reason for Change	OPI/SME
Nov 2020	**Updated**	**Gray**
Sep 2022	**Recommended enhanced screening for high risk aircrew changed from CT CACS to CTCA** **Lipid guidelines updated to reflect Ref E**	**Gray**

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BACKGROUND

1. Cardiovascular disease, and in particular coronary artery disease, remains a common medical problem resulting in restriction or grounding of CAF aircrew. Of particular concern from an aeromedical perspective, in individuals in the age range of aircrew, up to 60% of individuals do not have warning symptoms prior to their first major adverse cardiac event (MACE), and sudden cardiac death is often the first presentation.

2. Our understanding of the causes and mechanism of atherosclerotic disease continues to evolve. Classic risk factors including gender, age, lipids, smoking, hypertension, left ventricular hypertrophy and diabetes identify persons at higher risk of developing coronary atherosclerosis, but do not reliably identify coronary disease in particular individuals.

3. New conceptual models for atherosclerosis are evolving which identify vessel-wall injury as a prime mechanism, and in which inflammation plays an important role. The development of intravascular ultrasound has resulted in a clearer understanding of the evolution of atherosclerotic plaque from initial subendothelial inflammation to soft non-obstructive plaque which gradually progresses to flow-limiting obstructive lesions. Coronary events often occur as a result of the rupture of soft non-obstructive plaque with release of thrombokines which activate coagulation, resulting in abrupt occlusion. More gradual plaque build-up may progress to flow-limiting obstruction with silent ischemia or symptoms of angina, progressing to acute coronary syndromes.

4. Control of classic risk factors and associated life-style changes have had a significant impact on the incidence of coronary heart disease. As our understanding of atherosclerosis evolves, control of known risk factors should continue to be the goal. As new risk factors are identified, we will need to integrate these into our global approach for risk assessment and risk amelioration. Evolving risk factors include atherosclerotic lipid markers such as apolipoprotein B and lipoprotein (a), inflammatory markers including high-sensitivity C-reactive protein (hsCRP) and urinary microalbumin, and insulin resistance reflected in the metabolic syndrome.

5. This Guideline outlines the current approach for screening CAF aircrew for coronary disease, and intervention for those identified as being at increased risk. The approach in aircrew mirrors the most recent Canadian Cardiovascular Society (CCS) guidelines for the prevention of cardiovascular disease in Canadians (ref E), with the added flight-safety aspect of early detection of coronary disease before coronary events occur.

6. The two objectives of the **Aircrew CV Risk Screening Program** are:

   a. **Primary prevention**: Identification of individuals with risk factors which put them at increased risk for development of atherosclerotic coronary disease, with the implementation of appropriate risk-reduction intervention. This is particularly relevant in our aircrew population in whom identification of younger individuals at increased atherosclerotic risk for whom early risk reduction is especially important.

b. **Stratified screening**: identification of aircrew at high risk for a coronary event based on risk factors, with enhanced screening procedures to exclude the presence of asymptomatic coronary disease.

RISK FACTOR SCREENING

7. For Group A aircrew, risk data should be collected during type I medicals once every four years to age 40, then biennially (every two years) after age 40 IAW AMA 100-01. For Group B aircrew, risk screening should be done with the regular aircrew PHA (usually every 5 years). Fasting lipids are required only for initial aircrew selection medicals (to assess for metabolic syndrome which requires fasting glucose and triglycerides). For subsequent periodic aircrew medicals, fasting labwork is not required.

8. The following are required <u>in conjunction with Type I medicals</u> (based on the periodicity above).

a. Lipid profile:

i. Total cholesterol

ii. HDL cholesterol

iii. LDL cholesterol

iv. Triglycerides

v. Non-HDL cholesterol

b. Lipoprotein (a) (required once only. Result can be referred to in future re-evaluations without repeating each time).

c. A1C (a FBG is required on initial aircrew selection labs only)

d. Height, weight, BMI and waist circumference*

e. Blood pressure

f. ECG

g. Smoking history* – daily consumption of any tobacco product is a positive

h. Family history – A coronary heart event (heart attack or angina) in a first degree male relative under 55 or female relative under 65 is considered a positive family history*

* These items are collected at every PHA (both Type I and II)

CALCULATING CARDIOVASCULAR RISK:

Risk Estimate Equations

9. There are a large number of risk calculators available for cardiovascular risk including Framingham (FRS), Reynold's Risk Score, ASTROCHARM, and the American Heart Association ACVDRS. CFHS/Force Health Protection has developed a risk calculator based on the Framingham data, adapted for CAF personnel - the Framingham Cardiovascular Disease Risk Calculator/ FHP, Epidemiology Branch (herein abbreviated FHP/CDRC). (Link). For the purposes of these Guidelines, this is the recommended risk calculator. The FHP/CDRC includes a 30 year risk estimate, important for identifying increased risk in young individuals who would benefit from early risk intervention.

10. Using the FHP/CDRC, the risk data from Type I aircrew medicals should be inputted to calculate the individual's 10 year and 30 year risk. The 10 year risk is relevant in identifying high risk individuals who may need further screening for the presence of coronary disease (secondary screening), as well as risk intervention. The 30 year risk is helpful in identifying younger individuals who, although still at low immediate risk, would benefit from risk factor intervention.

CLASSIFYING RISK LEVELS

11. Based on the CDRC score and other risk factors, aircrew are classified in the following risk categories as follows

a. **High Risk**: Any of the following:

(1) CDRC risk ≥ 20%/10yrs

(2) Established diagnosis of atherosclerotic disease (including peripheral vascular disease- PVD)

(3) Presence of diabetes

(4) Chronic renal disease

(5) Individuals with intermediate CDRC risk ≥ 10% s any one of the following:

(a) Metabolic syndrome

(b) Family history of CAD in a first degree male relative ≤ 55 years of age or ≤ 65 years of age in a first degree female relative

(c) High-sensitivity C-reactive protein greater than 3 mmol/L

(d) Urine microalbumin/creatinine ratio > 2.5 in females, >3.5 in males

b. **Intermediate Risk:** Any of the following

(1) CDRC risk 10- 19%/10yrs

(2) Individuals with low CDRC risk < 10% plus the presence of

(a) Metabolic syndrome

(b) Family history of CAD in a first degree male relative ≤ 55 or ≤ 65 in a female relative

c. **Low Risk**

(1) CDRC risk < 10%/10yrs

ADDITIONAL RISK FACTORS

12. In addition to the classic risk factors – lipids, smoking, blood pressure, diabetes, certain additional markers have been shown to modulate cardiovascular risk. These include the inflammatory marker high sensitivity C-reactive protein (hs-CRP), urinary albumin-creatinine ration (ACR), as well as lipoprotein (a) [Lp (a)]. Additional risk factors also include family history, and the metabolic syndrome. For the purposes of this Guideline, in individuals found to fall in the Intermediate Risk category, these additional risk factors should be assessed for possible reclassification to high risk.

High Sensitivity-C Reactive Protein (hs-CRP)

13. CRP is an acute phase reactant produced by the liver in response to inflammatory cytokines such as interleukin-6. In the absence of systemic inflammatory conditions, high sensitivity CRP levels have been shown in multiple prospective trials to predict cardiovascular risk independent of FRS levels. For the purposes of these Guidelines, hs-CRP should be measured in individuals classified as Intermediate Risk based on a CDRC risk score of 10-19%. An elevated hs-CRP > 3mmol/L in an intermediate risk individual puts them in the high risk category. If an initial hs-CRP is elevated, it should be repeated since any inflammatory process may cause hs-CRP to be elevated.

Urine Albumin Excretion (UAE)

14. Urine albumin excretion is positively correlated across a continuum of values with adverse clinical outcomes, including cardiovascular disease. Microalbuminuria increases the risk for ischemic heart disease approximately two fold. A urinary albumin/creatinine ratio > 2.5 mg/mmol in women, and 3.5mg/mmol in men is considered abnormal, and reflects increased risk. The gender correction is for creatinine excretion related to muscle mass rather than a true gender effect. For aircrew classified as Intermediate Risk based on CDRC risk estimation (10-19%/10yrs), measurement of the urinary albumin/creatinine ratio is recommended. Increased UAE as reflected in an albumin/creatinine ratio greater than 2.5 in women or 3.5 in men puts intermediate risk individuals into the high risk category.

Family History

15. Genetic genotypes modulate cardiac risk, sometimes through identifiable risk factors such as a low HDL cholesterol or elevated Lp(a), but often through mechanisms that are not identified. For aircrew with a family history of definite ischemic heart disease (PCI or CABG, definite angina, myocardial infarction or sudden cardiac death) in a first degree male relative ≤ 55 years of age or ≤ 65 years of age in a first degree female relative, the calculated risk should be doubled.

Apolipoprotein B (ApoB)/ Non-HDL Cholesterol

16. Each of the atherogenic lipoprotein particles (V-LDL, intermediate LDL, LDL, and Lp[a]) contain one molecule of ApoB. ApoB levels reflect the total number of these atherogenic particles. Non-HDL-C is simply the difference between total and HDL-C. LDL measurements are not reliable for triglyceride levels greater than 1.5mmol/L, while Apo B and non-HDL cholesterol levels are not affected, and thus non-HLD or ApoB should be used for individuals with elevated triglyerides (>1.5mmol/L),

Lipoprotein (a) - Lp(a)

17. Lp(a) is an LDL particle in which apoB is attached to the apoA protein by a disulfide bridge. Plasma Lp(a) levels are determined by a single gene and heritability is ~ 90%. It structurally resembles plasminogen, and may impair fibrinolysis by competing with plasminogen. Lp (a) has been shown in most studies to be a strong predictor of premature atherosclerosis. There are currently no drugs to lower Lp(a). The CCS Guidelines (ref E) recommend measuring Lp(a) once in an individual's lifetime. For CAF aircrew, a single Lp(a) should be included during labs for an early (≤ age 40) type I AC PHA. An elevated Lp(a) elevates moderate risk to high risk, triggering secondary screening.

Metabolic Syndrome

18. The Metabolic Syndrome comprises a constellation of risk factors related to insulin resistance which include abdominal obesity, dysglycemia, elevated blood pressure, elevated triglycerides, and depressed HDL cholesterol. While there has been some controversy regarding the diagnostic criteria and mechanism of risk enhancement, there is consensus that the presence of the Metabolic Syndrome increases cardiovascular risk. Metabolic syndrome in CAF aircrew is covered in a separate Guideline for Flight Surgeons. For the purposes of this Guideline, the presence of the Metabolic Syndrome increases cardiac risk by one risk level. Metabolic Syndrome is defined here as three or more of:

a. Waist circumference >89cm in women or > 102 cm in men;
b. Triglycerides >1.70mmol/L;
c. HDL cholesterol < 1.3 mmol/L (women) or <1.0 mmol/L (men);
d. Fasting blood glucose equal to or greater than 5.7 mmol/L; and,
e. Blood pressure equal or greater than 130/85 mmHg.

RISK FACTOR INTERVENTION

19. A major goal of the aircrew cardiovascular risk screening program is to identify individuals at increased risk and initiate countermeasures. Intravascular ultrasound studies have shown that atherosclerotic plaque can be reversed by intensive risk factor reduction.

Treatment with statin results in a 30% decrease in estimated risk reduction. It is particularly important to identify and initiate risk reduction in younger aircrew who have elevated long-term risk as reflected in the 30 year FHP/CDRC score, but who may have a low 10 year risk score because of their age.

Smoking Cessation:
20. Smoking cessation should be encouraged and reinforced at every opportunity. Health care provider intervention has been confirmed as efficacious. Aircrew may use transdermal nicotine patches without a flying restriction. Treatment with bupropion or varenicline requires operational flying restrictions and close monitoring. Details of smoking cessation therapy for aircrew are outlined in the FSG 1900-01 Medications and Aircrew.

Blood pressure:
21. Blood pressure should be assessed and intervention initiated as per Canadian Hypertension Society clinical guidelines . Except in the case of a hypertensive emergency or with severe hypertension (>180/110), most aircrew do not require grounding during initial assessment. Most anti-hypertensive medications are compatible with unrestricted aircrew duties (except during initiation and stabilization), and treatment should not be delayed or postponed because of aircrew status (see also FSG 1900-01– Medications and Aircrew).

Dyslipidemia
22. Dyslipidemia: Treatment of dyslipidemia should follow current Canadian Cardiovascular Society guidelines (Ref E).

a. Treatment recommendations begin with life-style changes including healthy eating habits, maintenance of a healthy weight, and regular physical activity.

b. Pharmacotherapy thresholds and treatment targets are based on risk stratification (See Risk Levels- above) and are outlined in the table below. Pharmacotherapy is based on statins, with atorvastatin or rosuvastatin being preferred over lower efficacy statins. To achieve treatment targets, a cholesterol absorption inhibitor (e.g. ezetimibe) may be additionally required. Statins and ezetimibe are acceptable in aircrew with appropriate monitoring. For aircrew intolerant to statins or who fail to reach treatment targets on a statin +ezetimibe, PCSK9 inhibitors such as evolocumab, (Repatha) may be considered and are acceptable for aircrew duties. Table I below summarizes the CCS guidelines (not fully comprehensive- see the Reference for full details)

Risk Level	10-yr	Treat when	Treatment Targets
High	≥ 20%	All	- LDL-C < 2.0 mmol/L or > 50% decrease in LDL - ApoB < 0.8 g/L - non-HDL<2.6
Intermediate	10-19%	- LDL-C ≥ 3.5 mmol/L or - non-HDL ≥ 4.2 - ApoB>1.05 g/L OR intermediate risk plus M>50,F>60 with+1 risk factor (IFG, smoker, HTN, ↑WC,low HDL) OR intermediate risk With other risk modifiers (CACS>0, FHx+, hs-CRP>2,	LDL < 2.0 or Non>HDL <2.6 or -> 50% decrease in LDL Apo B <0.85g/L
Low	<10%	- LDL-C ≥ 5.0 mmol/L or non-HLD≥5.8 or apoB≥1.45 (familial hyperlipidemia)	LDL<2.0 or Non-HDL>2.6 Or >50% LDL reduction ApoB<0.85

Table I: CCS-based recommendations for Primary Prevention

Other Risk Factors:

23. Investigation and treatment of insulin resistance with diabetes or the metabolic syndrome in aircrew is covered in a separate Guideline. Treatment often involves multiple risk factor intervention. Again, aggressive preventive intervention is preferred to a minimalist approach, which often eventually results in loss of aircrew status once a cardiovascular event has occurred.

SECONDARY SCREENING FOR CORONARY DISEASE

24. Aircrew identified as being in the “High Risk” category require additional screening for asymptomatic coronary heart disease. There are a variety of testing modalities available for screening for asymptomatic coronary disease including a) exercise stress testing – either with or without imaging (echo or nuclear perfusion imaging), and b) imaging technologies including CT coronary angiography (CTCA) and CT coronary artery calcium scores (CT CACS).

25. Exercise testing, with or without imaging can only detect coronary lesions that produce ischemia (hemodynamically significant). However, most coronary events in aircrew occur as a result of plaque rupture in <u>non</u>-hemodynamically significant atherosclerotic lesions. Thus, exercise stress testing with or without imaging is NOT recommended for screening asymptomatic aircrew for underlying coronary disease. These functional tests

should be reserved to assess for inducible ischemia in aircrew already identified as having coronary atherosclerosis on imaging

26. For CAF aircrew identified to be in the high-risk category for coronary disease, further assessment for the presence of asymptomatic coronary heart disease is required. Cardiac CT technologies (both CT CACS and CTCA) are evolving and require less radiation than previous-generation technologies. Although CT CACS is a mature technology which identifies calcified coronary plaque and provides good stratification for the risk for a coronary event, not all plaque is calcified, and even with a CACS=0 there is a small but significant risk (from an aeromedical perspective) for a plaque rupture acute coronary event. CTCA is increasingly able to identify features of vulnerable plaque. Thus, **for enhanced screening for high risk aircrew, a CTCA (with CACS if available) is the preferred procedure**.

27. CTCA either alone or with CACS is available at many civilian CT facilities across Canada. The requisition should specify that the test is being requested for occupational screening of a CAF aircrew member identified as being at high risk for coronary disease.

28. CT CACS scores reflect the burden of calcified atherosclerotic plaque, reported as Agatston units. Any score greater than zero indicates the presence of coronary plaque, with increasing scores reflecting greater plaque burden. In general, the following ranges guide disposition of coronary calcium scores

a. **0-100** - coronary atherosclerotic plaque is present, but is unlikely to be hemodynamically significant. Risk reduction is indicated, including, in most cases, a statin. Smoking cessation is mandatory for continuing aircrew duties with a CACS>0

b. **100-400** - Increased risk for a hemodynamically significant lesion. Intensive risk reduction is indicated including statins, to target LDL < 2.0mmol/L. CTCA is required. Exercise testing with imaging (stress echo or nuclear perfusion) should be arranged to assess for inducible ischemia.

c. **>400** - High probability of a hemodynamically significant lesion. CT or invasive coronary angiography is required, along with exercise stress testing with imaging to assess for inducible ischemia. Intense risk reduction of all modifiable risk factors, including treatment with statins, ezetimibe, and if required, PCSK9 inhibitors (eg evolocumab/Repatha) to target LDL <1.8

29. CTCA identifies the presence of atherosclerotic lesions within the coronary artery lumen, both calcified and non-calcified. CTCA technologies are evolving and increasingly may identify vulnerable plaque predisposed to rupture. CTCA identifies all coronary endovascular lesions that impinge on the coronary lumen, including those that are obstructive (>50% stenosis), and those that are likely to be hemodynamically significant, ie impair blood flow (usually > 70%). Hemodynamically significant lesions may require a revascularization procedure (PCI or CABG) if inducible ischemia is identified. For non-hemodynamically significant lesions, the risk for a coronary event is related to the overall plaque burden, which for coronary angiography is defined by the sum of all identified lesions. The following classification applies

a. Normal. No coronary lesions identified

b. Minimal (MinCAD). Sum of all lesions <50%

c. Moderate (ModCAD). Sum of all lesions <120%. No lesion >70%, ≤1 lesion >50%

d. Severe (SCAD). Sum of all lesions >120%, presence of >70% lesion or >1 lesion >50%

DISPOSITION OF AIRCREW DURING INVESTIGATION AND INTERVENTION FOR CORONARY ARTERY DISEASE

30. An operational flying restriction is generally not required during periodic risk screening and stratification. Interventions for risk factor modification may require a brief grounding or restriction during initiation of therapy, e.g. with anti-hypertensives, anti-dyslipidemics, or smoking cessation aids (See FSG 1900-01 – Medications and Aircrew).

31. Unless there is a high level of suspicion (e.g. angina or related symptoms), aircrew need not be grounded during investigation of individuals classified as high risk. If enhanced screening (CTCA ±CACS) indicates the presence of coronary disease, aircrew may require grounding while additional investigation and/or intervention is arranged based on clinical indications. A temporary G4(T6) A7(T6) should be initiated.

32. Return to flying status after investigation of aircrew who are found to have significant coronary atherosclerosis demonstrated by CT imaging/angiography is covered in FSG 600-02.

Figure 1: CAF CAD Screening and Evaluation Algorithm