Management of established coronary artery disease in aircrew without myocardial infarction or revascularisation

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ABSTRACT

This paper is part of a series of expert consensus documents covering all aspects of aviation cardiology. In this manuscript, we focus on the broad aviation medicine considerations that are required to optimally manage aircrew with established coronary artery disease in those without myocardial infarction or revascularisation (both pilots and non-pilot aviation professionals). We present expert consensus opinion and associated recommendations. It is recommended that in aircrew with non-obstructive coronary artery disease or obstructive coronary artery disease not deemed haemodynamically significant, nor meeting the criteria for excessive burden (based on plaque morphology and aggregate stenosis), a return to flying duties may be possible, although with restrictions. It is recommended that aircrew with haemodynamically significant coronary artery disease (defined by a decrease in fractional flow reserve) or a total burden of disease that exceeds an aggregated stenosis of 120% are grounded. With aggressive cardiac risk factor modification and, at a minimum, annual follow-up with routine non-invasive cardiac evaluation, the majority of aircrew with coronary artery disease can safely return to flight duties.

INTRODUCTION

Coronary artery disease (CAD) is the leading cause of death globally, currently accounting for 17 million deaths per year, and projected to increase to more than 23 million by 2030.1 CAD is also the leading cause of denial, or withdrawal, of flying privileges in both civilian and military aircrew. The consequences of coronary angiographic findings are different in aircrew compared with the general population, and consideration for continuing flight duties of aircrew with known CAD requires a detailed aeromedical review by a cardiac specialist with aviation medicine experience. This assessment must incorporate angiographic findings, a detailed risk assessment and a nuanced management plan that must include aggressive control of the atherosclerotic disease process to ensure safety of flight.2

Current published guidelines regarding CAD treatment should always be followed initially for all aircrew however, there may be occupational considerations that require a more aggressive treatment approach for which aircrew consent is required. For example, a single stenosis >70% in an asymptomatic patient can either be treated medically or revascularised based on current guidelines but only the latter would be acceptable for a pilot to return to flight duties, to mitigate the longer term risks, including sudden incapacitation. In the past decade, because of advanced intervention and secondary prevention, there has been a steady increase in return to flight for aircrew who would previously have been permanently disqualified from all flying duties.3

Detection and risk determination of CAD in aircrew

There is increasing recognition that non-obstructive CAD and overall atheroma burden are part of a risk continuum and are associated with higher event rates and increased risk of death.3 This is particularly important in the risk assessment of aircrew, many of whom are young and undertaking routine high hazard activities in which incapacitation or distraction may prove catastrophic.4 In military aircrew, this may be further compounded by operating in a hostile environment with limited access to health facilities and sometimes in high performance aircraft with additional haemodynamic consequences. For example, a 50% stenosis may demonstrate no ischaemia on a full Bruce exercise protocol, but theoretically may still cause ischaemia under 9 G in a fighter aircraft.

1Evidence based cardiovascular risk assessment in aircrew poses significant challenges as data to support decision making at the low level of tolerable risk in aviation is rarely available from the published literature. As a result, there are discrepancies between aviation authority’s recommendations in different countries, and even between licensing organisations within single countries. The NATO HFM-251 Occupational Cardiology in Military Aircrew working group is constituted of full time aviation medicine and aviation cardiology experts who advise both their militaries and civil aviation organisations, including, but not limited to, the Federal Aviation Administration (FAA), Civil Aviation Authority (CAA), European Aviation Safety Agency (EASA) and National Aeronautics and Space Administration (NASA). The recommendations of this group are as a result of a 3 year working group that considered best clinical cardiovascular practice guidelines within the context of aviation medicine and risk principles. This work was conducted independently of existing national and transnational regulators, both military and civilian, but considered all available policies, in an attempt to determine best evidence based practice in this field. The recommendations presented in this document, and associated manuscripts, are based on expert consensus opinion of the NATO group. This body of work has been produced to develop the evidence base for military aviation cardiology and to continue to update the relevant civilian aviation cardiology advice following the 1998 European Cardiology Society aviation cardiology meeting.
The key question for aeromedical examiners, flight surgeons, aviation cardiologists and aeromedical licensing authorities is what level of CAD increases the occupational risk to beyond an acceptable level. This requires an integration of the aeromedical and risk assessment (ie, angiographic data, non-invasive testing and risk factor mitigation) with the particular aircrew role (pilot, other aircrew, military, civilian, etc). For professional dual pilot operations, the current accepted level of risk is generally a risk of incapacitation <1% per annum, while for fast jet or single seat pilots (either fixed wing or rotary) this may be much lower. For other mission critical, but non-flight critical, aircrew the acceptable risk may be greater. However, evidence based risk assessment of these individuals poses significant challenges in the aviation environment as data to support decision making at this low level of risk are rarely available in the published literature. As a result, there are discrepancies between aviation authorities in different countries, and even between licensing organisations within a single country.

The atherosclerotic continuum and risk in aircrew

CAD is known to be a progressive disease whereby established coronary plaque progresses and/or new plaques are formed. Plaques may be characterised by constituent components (ie, calcified plaques, non-calcified plaques or mixed plaques) or by vulnerability (stable vs unstable). Plaque vulnerability is associated with mixed or non-calcified plaques, with inflammatory cell infiltrates that result in increased likelihood of plaque rupture and coronary thrombosis (with a resultant acute coronary syndrome). This vulnerable plaque can be found in a vessel with a stenosis that, if stable, would not usually cause symptoms, ischaemia or be recommended for revascularisation. Increased coronary artery calcification is associated with increased likelihood of cardiovascular events as it is a marker for established coronary atheroma (coronary artery calcium burden is usually about 20% of overall atheroma burden), but calcified plaques are usually stable and usually cause symptoms due to flow limitation rather than acute rupture. Aircrew may be found to incidentally have CAD after occupational screening, or from atypical unrelated symptoms with no evidence of ischaemia, myocardial infarction or revascularisation. However, a new diagnosis of CAD declares an increased risk of sudden incapacitation in aircrew, and is always relevant even if mild. The detail of the term major adverse cardiovascular event (MACE) is specific to an individual study but most commonly refers to a combined endpoint of death, myocardial infarction and revascularisation (or repeat revascularisation). Death or myocardial infarction may clearly lead to sudden incapacitation but the need for revascularisation also describes individuals who are at risk of coronary artery lesions capable of causing both limiting symptoms and/or sudden incapacitation. For the purpose of aircrew disposition, we therefore use risk of MACE as a marker of risk for sudden incapacitation.

Historic pathological studies suggest that a 30–40% luminal stenosis is enough to precipitate a fatal coronary event, likely secondary to rupture of ‘vulnerable’ plaque (discussed above). Currently, no imaging modality, invasive or non-invasive, can accurately and reliably identify vulnerable plaque, although this is an area of intense research, especially in cardiovascular CT, MRI and nuclear positron emission tomography imaging. The occupational ramifications of this for aircrew are self-evident, given that any degree of CAD disease, including non-obstructive plaque and/or the presence of coronary artery calcium, increases the risk of sudden incapacitation. Given the potential career ramifications, a diagnosis of ‘presumed’ or ‘suspected’ CAD, based on risk scores, or standard 12 lead or exercise ECG testing, should be avoided. Anatomical verification via angiography (CT coronary angiography (CTCA) or invasive coronary angiography ICA)) is required by the aviation cardiologist to confirm the presence and extent of CAD (degree of stenosis or lack thereof) for regulatory authorities for whom they work and advise, whether civilian or military. Table 1 describes the degrees

### Standards

#### Table 1 Coronary artery disease classifications for aeromedical disposition

| Stenosis (%) | FFR | Annual MACE (%) | Pilot aircrew disposition | Non-pilot aircrew disposition* |
|--------------|-----|-----------------|---------------------------|-------------------------------|
| Haemodynamically significant ≥70 | <0.8 | >3.0 | Grounded† | Grounded† |
| Single vessel obstructive (non-haemodynamically significant) 50–69 | >0.8 | 1.0–3.0 | With restrictions†§ | Unrestricted possible‡* |
| Single vessel non-obstructive 30–49 | >0.8 | 1.0–3.0 | With restrictions† | Unrestricted possible* |
| Luminal irregularities Up to 30 | >0.8 | 0.5–1 | Unrestricted possible‡ | Usually unrestricted * |
| Aggregate stenosis: severe ≥120 | N/A | >3.0 | Grounded† | With restrictions†* |
| Aggregate stenosis: moderate 50–119 | N/A | 1.0–3.0 | With restrictions† | Unrestricted possible‡* |
| Aggregate stenosis: mild <50 | N/A | 0.5–1.5 | Unrestricted possible‡ | Unrestricted possible* |
| Left main stenosis: significant 30–49 | N/A | 1.0–3.0 | With restrictions†§ | Usually with restrictions‡§* |
| Left main stenosis ≥50 | N/A | >3.0 | Grounded† | Grounded† |

*Will depend on aircrew role and individual agency acceptable risk threshold.
†Without revascularisation; return to flight (in a limited capacity) may be possible after revascularisation.
‡With aggressive risk factor modification and close follow-up, restricted return to flight duties may be possible depending on the risk threshold accepted by the individual aircrew’s respective regulatory authority.
§Wide discrepancy in disposition in difference agencies. Federal Aviation Administration would allow for flight duties with restrictions, European Aviation Safety Agency would permanently ground aircrew.

FFR, fractional flow reserve; MACE, major adverse cardiovascular event.

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*Aircrew are defined somewhat differently in civil and military aviation. NATO and the International Civil Aviation Organisation (ICAO) delegates the definition of aircrew to national authorities. In the civilian sector, aircrew are often categorised as flight crew (pilots)/technical crew members and cabin crew, with separate regulation for air traffic controllers. The medical define aircrew more broadly as ‘persons having duties concerned with the flying or operation of the air system, or with passengers or cargo when in flight’. From a risk perspective, professional (commercial) pilots have a higher attributable risk than private pilots and non-pilot aircrew. Controllers are considered to have an attributable risk equivalent to professional pilots. From a cardiovascular perspective, aircrew whose flying role includes repetitive exposure to high acceleration forces (Gz) comprise a subgroup who, due to the unique physiological stressors of this flight environment, often require specific aeromedical recommendations. A more detailed description of aircrew is available in Table 1 (Nicol ED, et al. Heart 2018;105:s3–s8. doi:10.1136/heartjnl-2018-313019).
of CAD, as commonly defined in the literature, with associated aircrew risk and aggregate stenosis defined in aircrew with occupational ramifications (further described below). In this paper, stenosis severity is defined by maximal luminal diameter stenosis, although it is well recognised that area stenosis (which can be determined on CT angiography) is often much greater.

HAEMODYNAMICALLY SIGNIFICANT CAD

As with the non-aircrew population, the degree of CAD in aircrew is often based on degree of luminal diameter stenosis seen on angiography (CTCA or ICA). For aeromedical purposes, a single coronary lesion (outside the left main stem (LMS) or proximal left anterior descending coronary artery) with any gradable stenosis up to 49% is graded as mild, 50–70% is considered moderate, 71–90% severe and 91–100% critical.11 Anatomically, obstructive disease is generally considered to be one or more lesions of 50% or greater diameter reduction while a 70% or greater stenosis is also considered flow limiting or haemodynamically significant and most likely to cause ischaemia during stress. There is a wide discrepancy between qualitative angiographic grading and flow limitation; ischaemia is a physiologic assessment that cannot be made by angiography alone, unless performed in conjunction with fractional flow reserve (FFR).11 Given CAD with ischaemia has a worse prognosis, we recommend ischaemic evaluation in aircrew with any lesion that causes a stenosis of >50%. This assessment can be based on non-invasive studies, such as stress echocardiogram, cardiac MRI and nuclear perfusion imaging (single photon emission CT or positron emission tomography), or measured utilising FFR.11 FFR (traditional or instantaneous wave-free ratio) is particularly helpful in aircrew to verify a significant decrement in flow (FFR <0.80) confirming haemodynamic significance, regardless of severity of stenosis. The rapid development of CT derived FFR offers the potential for non-invasive functional data to be incorporated into both clinical and occupational guidelines in due course. As with ischaemic or anatomically high risk (haemodynamically significant) lesions, a positive indication of reduction in flow reserve on FFR CT that is not revascularised is likely to result in withdrawal of flying privileges in all professional flying activity.

Although much controversy exists regarding optimal medical therapy alone versus revascularisation outside the setting of acute coronary syndrome, there are some data to support revascularisation (with decreased MACE) in haemodynamically significant stenoses.12 In ischaemic disease, with or without symptoms, there is similar controversy but some data suggest lower all cause mortality using percutaneous coronary intervention (PCI) compared with optimal medical therapy during a mean follow-up of 3.0 years.13 In order to return to flying duties, aircrew with haemodynamically significant stenosis, with associated ischaemia, require revascularisation (coronary artery bypass graft (CABG) or PCI) in addition to optimal medical therapy, regardless of symptomatology.(online supplementary file 1).

| Table 2 | Haemodynamically significant CAD |
|-----------------|-----------------|
| Aircrew with haemodynamically significant stenosis with associated ischaemia require revascularisation (CABG or PCI) regardless of symptomatology to return to flight |
| Strongly recommended |

Obstructive CAD

Data suggest that obstructive CAD (any single stenosis of >50%) confers a >1% per annum of MACE, the threshold often used for withdrawal of professional pilot licenses in dual crew operations.2 Aggressive risk factor modification along with good functional status significantly decreases mortality (to as low as 0.25% per year) and myocardial infarction rates (to <1% over 4 years) allowing for return to limited flight duties in some aircrew.14 In obstructive disease, consideration should be given to ruling out ischaemia (haemodynamic significance) in all patients with a lesion of 50% or greater, either via perfusion imaging and/or FFR. Those aircrew with obstructive, but non-flow limiting, disease (50–69% stenosis and/or FFR >0.8), present the greatest occupational challenge. Current clinical evidence suggests that there are only two indications for revascularisation; prognostic benefit (decreased mortality) secondary to treating a demonstrable ischaemic burden of >10% of the myocardium or for symptom relief. Many aircrew with 50–69% stenoses, or rarely even a single >70% stenosis with an associated FFR >0.8, do not meet these criteria and find themselves breaching the minimal acceptable risk for aircrew operations, but with no clinical justification for intervention/revascularisation.

In addition to maximal stenosis severity, it is clear from published data that the total burden of disease is also important. Historic data from the Coronary Artery Surgery Study (CASS) Registry (ICA) and more recently the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) registry (CTCA) demonstrates decreasing survival rates as the number of diseased vessels increases, with >90% survival with single vessel disease versus 40% survival with three vessel disease up to 12 years of follow-up.15 16 Therefore, pilots with more than one 50% stenosis, or a high non-obstructive disease burden (see aggregate stenosis below), are not recommended to return to flight duties. Other (non-pilot) aircrew require a careful risk assessment, including risk mitigation interventions to assess suitability for aircrew operations.

Obstructive, single vessel CAD, without ischaemia, and not deemed haemodynamically significant, is still incompatible with pilot duties and breaches the traditional ‘1% rule.’ However, with aggressive risk factor modification and close follow-up, restricted return to flight duties may be possible depending on the risk threshold accepted by the individual aircrew’s respective regulatory authority. For non-pilot aircrew, a more flexible approach may be appropriate with a greater risk being acceptable.2

| Table 3 | Obstructive CAD |
|-------------|-------------|
| Pilots with more than one 50% stenosis are likely to have MACE event rates >1% per annum and are not recommended to return to unrestricted flight duties. Other aircrew require careful risk assessment, including risk mitigation to assess a possible return to aircrew duties |
| FFR during invasive angiography should be considered in all lesions with >50% stenosis to determine if haemodynamically significant |
| Aircrew with obstructive, single vessel CAD, without ischaemia, and not deemed haemodynamically significant, may be returned to restricted flight duties with aggressive risk factor modification and close follow-up |
| Not recommended |
| Strongly recommended |
| Consider |

Non-obstructive CAD

Numerous large clinical ICA and CTCA datasets have demonstrated an increased risk of MACE in symptomatic patients with non-obstructive CAD.17 18 However, few data exist for asymptomatic individuals as they have no clinical justification for undergoing investigation. Historical long term studies of aircrew with non-obstructive (<50% stenosis) CAD in the USA and UK report low annual cardiac event rates (in the US 0.6%
and 0.4% per annum at 5 and 10 years, respectively, with no cardiac deaths, and in the UK a 92% survival at 10 years. Non-invasive functional test results (abnormal exercise ECG or thallium myocardial perfusion scintigraphy) at the time of index ICA did not predict future cardiovascular disease events or survival; however, classic cardiovascular risk factors and the extent of non-significant CAD at ICA (as well as coronary calcification noted on fluoroscopy) did predict future events. This mirrors more recent published data and underpins the increasing clinical interest in atherosclerotic disease burden and risk mitigation interventions, as opposed to pure luminal stenosis assessment. Aviation medicine concerns in non-obstructive CAD include the fact that many fast jet, high performance and rotary aircraft are often flown in a single seat configuration. Flying high performance airframes also increases cardiac demand due to the high +G_1 environment, and the effect on vascular plaque disease is largely unknown. Perhaps the most worrisome concern in aircrew is the understanding that acute events (ie, plaque rupture and subsequent myocardial ischaemia/infarction) often occur in those with non-obstructive CAD, and that asymptomatic progression to significant disease and death may occur unheralded.

While untreated, non-obstructive CAD may confer a >1% annual risk of MACE, aggressive secondary risk factor modification and monitoring likely reduces this risk below the 1% threshold, allowing maintenance of limited flying privileges. It is paramount that compliance with primary coronary event prevention is ensured with regular investigation of lipid and blood pressure profiles and disqualification strongly considered if risk factor goals are not met. Finally, lesions in the LMS are higher risk and thus treated more cautiously. A single 30–49% LMS should be treated as obstructive disease in aircrew.

### Aggregate stenosis

In addition to the assessment of single stenosis severity, aggregate stenosis and total atheroma burden are also known to be of critical importance in the determination of future MACE and death. In the US Air Force (USAF) pilot population, severe coronary artery disease was initially defined as any single stenosis >50% with an annual MACE annual event rate of 2.2% for those with a maximal lesion >50% stenosis. To allow for a better understanding of the distribution of events in these cohorts, an aggregate stenosis was developed using a summation of all stenoses. When the aggregate stenosis was <50%, there was a 0.6% annual rate of MACE, between 50–120% aggregate a 1.1% annual risk, and >120% a 3% annual risk of MACE. Multivariate analysis showed this aggregate stenosis to be a better predictor of MACE than family history, coronary calcium or maximum lesion >50%. A few caveats were found; any single stenosis >70%, two stenoses >50% and/or left main stenosis >50% all demonstrated over 3% annual MACE regardless of aggregate and are not permitted to fly in the USAF. In the civilian aviation environment, the UK Civil Aviation Authority does not permit professional flying privileges in those with two or more lesions between 30% and 50%, and in the USAF, flight restrictions are required when aggregate stenosis is >50%.

Limiting aircrew to non-high performance and dual piloted aircraft with another qualified pilot should be considered for all professional pilots with ≥50% aggregate stenosis.

### Table 5 Aggregate stenosis

| Aggregate stenosis | Strongly recommended | Table 5 Aggregate stenosis

| Aggregate stenosis | Strongly recommended |
|--------------------|----------------------|
| Aircrew with ≥50% aggregate stenosis should be limited to non-high performance aircraft. Pilots should further be restricted to dual pilot operations |

At the least severe end of the spectrum of CAD, is luminal irregularity, defined on angiography as irregular arterial edges due to atherosclerotic plaque, but gradable at <30% luminal stenosis (diameter reduction) and is usually evident throughout all coronary arteries. While few data exist for outcomes in patients with luminal irregularity in the general population, data from USAF aircrew demonstrate cardiac event rates of 0.5% per year over 10 years, which although low, is still 5 times the 0.1% per year event rate seen in military pilots with truly normal coronary angiography.

Coronary calcium scoring (CACS) also appears to serve as a good surrogate of aggregate stenosis. In a study of USAF aircrew, luminal irregularities correlate to a CACS of 10–99 and event risk of approximately 0.5% per year, while a coronary calcium score >100 correlates to an aggregate stenosis of >50% with a >1% annual risk of MACE. The CTCA CONFIRM registry shows a similar correlation between CACS and stenosis severity, and evidence that non-obstructive CAD is associated with an increased risk of MACE. In the CONFIRM registry, there was no significant differences in all cause mortality in patients with a CAC score of 0, irrespective of obstructive CAD on angiography, but recent data from UK military aircrew demonstrated that 4% of aircrew with a CACS of 0 had stenosis >50% on CTA. Aggressive risk factor modification and regular follow-up is thus paramount for any amount of quantifiable CAD in aircrew, including isolated luminal irregularities and/or the presence of any coronary calcium. A summary of guidance on stenosis severity can be found in Figure 1.

### Importance of Aggressive Risk Factor Modification in Aircrew

Estimated risk for MACE is likely to be overestimated based solely on anatomical imaging. Therefore, in aircrew, imaging based risk estimates may be modulated downwards to reflect risk reduction from pharmacological intervention and exercise. The likelihood of a MACE is lessened by approximately 10% per mmol reduction in low density lipoprotein cholesterol (LDL), regardless of the initial LDL level, and at all levels of coronary atherosclerosis. There is no lower threshold for this effect and statins safely reduced both LDL and plaque inflammation and are recommended in aircrew. While newer promising agents are emerging that further reduce LDL (PCSK-9 inhibitors) and target inflammation (interleukin-1β) and cholesterylester transfer protein inhibitors, they all have limited safety data and are generally not recommended in aircrew. However, if no alternative is available, they should be used cautiously in aircrew, with careful and regular oversight. Exercise also significantly, and proportionally, reduces risk of MACE beyond aggressive management of traditional risk factors, likely due to a positive effect on vascular endothelial function. The International Space Station Medical Board incorporates these risk reductions (of up to 50%, based on optimal LDL, exercise and physical fitness (metabolic equivalents (METs))), and these should be
incorporated (with agency agreed values) into organisational risk matrices when determining aeromedical disposition of aircrew with angiographically confirmed disease. Without adherence to recommended risk reduction interventions, ongoing risk for major adverse cardiac events will increase, and in many cases is likely to exceed the acceptable risk for return to flight for aircrew duties.

### DISCUSSION

Recent advances in our understanding of the mechanism of coronary atherosclerosis and resulting MACE is changing our appreciation of the risk associated with anatomic lesions. New medical approaches to modifying the development and characteristics of coronary plaque are resulting in significant reductions in the risk for MACE in individuals with demonstrated plaque.

Recent FFR data are also challenging the paradigm of classifying significant disease as >/50% stenosis as it has been shown that individuals may have functionally significant lesions with as little as 30% luminal narrowing, while many with >50% stenosis and some with >70% do not. Additionally, recent evidence from CTCA suggests that there is a strong correlation between plaque morphology with functional significance compared with CT and traditional invasive FFR. This apparent dichotomy of stenosis, plaque burden and functional significance is likely due to a far more complex set of physiological parameters being required to truly determine functionally significant lesions. It is therefore imperative that aggressive risk factor modification be made mandatory for all aircrew with any degree of CAD.

### CONCLUSION AND RECOMMENDATIONS

Established CAD of any degree in aircrew requires ongoing clinical and diagnostic evaluation and therapeutic intervention that should continue long after diagnosis. While most major national/international cardiology guidelines argue against routine non-invasive cardiac evaluation in asymptomatic individuals, even with known cardiovascular disease, these guidelines do not take into account high risk occupations such as aircrew. Regular follow-up and cardiac evaluation in aircrew with...
established, non-obstructive CAD is prudent to ensure flight safety. It is recommended that at a minimum, annual follow-up with a primary care provider and/or cardiologist is undertaken with close attention paid to primary prevention of MACE and ensuring prevention compliance. Failure to adhere to preventive guidelines should result in withdrawal of flight privileges.

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