Coronary Artery Disease Screening Using CT Coronary Angiography

Randy Wang Long Cheong; Brian See; Benjamin Boon Chuan Tan; Choong Hou Koh

BACKGROUND: The increased utility of CT coronary angiography (CTCA) in cardiovascular screenings of aircrew has led to the increased detection of asymptomatic coronary artery disease (CAD). A systematic review of studies relevant to the interpretation of CTCA for the occupational fitness assessment of high-risk vocations was performed, with findings used to describe the development of a pathway for the aeromedical disposition of military aviators with asymptomatic CAD.

METHODS: Medline was searched using the terms "CT coronary angiogram" and "screening" and "prognosis". The inclusion criteria were restricted to study populations ages > 18 yr, were asymptomatic, were not known to have CAD, had undergone CTCA, and with their associations with major adverse cardiovascular events (MACE) and other relevant cardiac outcomes reported.

RESULTS: Included in this systematic review were 10 studies. When compared to subjects with no or nonobstructive CAD, those with obstructive CAD on CTCA had hazard ratios (HR) for cardiac events ranging from 1.42 to 105.48. Comparing subjects with nonobstructive CAD and those without CAD on CTCA, a lower HR of 1.19 for cardiac events was found. The annual event rates of subjects with no CAD on CTCA were extremely low, ranging from 0 to 0.5%.

CONCLUSIONS: Based on the findings, we suggest that CTCA should only be performed in aircrew with higher cardiac risk profiles. Those found to have no CAD or minimal CAD (i.e., ≤ 25% stenosis) in a non-left main coronary artery on CTCA can be returned to flying duties. All other results should be further evaluated with an invasive angiogram.

KEYWORDS: CT coronary angiography, cardiovascular screening, military aircrew.

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Medical screening of aircrew began in World War I, with potential pilots made to undergo physical examinations to determine their fitness for flying.[21] Following the founding of the International Civil Aviation Organization (ICAO) in 1947 and publication of the ICAO "Manual of Civil Aviation Medicine" in 1974, the medical fitness requirements for pilots were laid out in greater detail. Cardiovascular assessments were initially rudimentary, mandating a simple resting electrocardiogram, blood pressure measurement, and on occasion, a treadmill electrocardiogram.[12]

Technological leaps in cardiac imaging modalities in the past two decades have resulted in more accurate and sensitive detection of underlying occult cardiac conditions that would otherwise have not been detected in the past.[10] Significantly, the improved temporal and spatial resolution of computer tomographic scans, coupled with a decrease in minimum radiation exposure, have enabled coronary vessel anatomy to be delineated in greater detail and in a safe, noninvasive manner. The increase in the use of CT coronary angiography (CTCA) for pre-employment and in-service cardiovascular screenings has led to new challenges in determining the aeromedical disposition of aircrew, predominantly from the increased detection of asymptomatic coronary artery plaque disease across a spectrum of severity.[18]

There remains a lack of guidance from most modern military and civilian aeromedical licensing authorities on how CTCA results should guide aeromedical disposition for both

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military and civilian aircrew.[20,22,23] Thus, the aims of this paper are twofold: first, to perform a systematic review of existing studies relevant to the interpretation of CTCA for the occupational fitness assessment of high-risk vocations; and second, to describe our development of a pathway for the aeromedical disposition of military aircrew with asymptomatic coronary artery disease (CAD).

METHODS

This review was conducted in accordance with the preferred reporting items for systematic reviews and meta-analysis (PRISMA).[16] No published study protocol currently exists. We searched Medline for studies on human subjects published in English from the inception of the database until June 2019. The search terms used were "CT coronary angiogram" and "screening" and "prognosis." The reference lists of included studies were hand-searched for additional eligible articles. The results of the review were used to derive a pathway for the aeromedical management of military aircrew with asymptomatic CAD.

All titles and abstracts that were identified by the search were screened for inclusion. Studies that were obviously irrelevant as determined by their titles and abstracts were excluded. The inclusion eligibility of the remaining articles was assessed based on the PICOS criteria, and only studies that met the set inclusion criteria were included in the review. The inclusion criteria were restricted to study populations ages $>$ 18 yr, were asymptomatic, were not known to have CAD, had undergone CTCA, and with their associations with major adverse cardiovascular events (MACE) and other relevant cardiac outcomes reported. We included prospective and retrospective studies, but excluded meta-analyses, case reports, editorials and letters to the editor, conference abstracts, and book chapters. The following information from each included study was extracted: author, year of study, study design, sample size, imaging results, events (all-cause mortality or cardiac death, nonfatal myocardial infarction, unstable angina pectoris, revascularization). Given the heterogeneity of the data, a meta-analysis was not performed as part of this review.

RESULTS

The search returned 868 studies, of which 842 were classified as ineligible based on titles or abstracts (**Fig. 1**). Out of the remaining 26 full texts, 6 studies were included for the systematic review. An additional four studies were included by searching the reference lists of the included articles. The review contained a total of 10 studies.

The 10 included studies comprised prospective and retrospective observational studies. The studies were published between 2008 and 2017. The included studies looked at MACE, such as cardiac death, nonfatal MI, unstable angina, and late revascularization, as the outcomes. All studies defined obstructive CAD as a coronary artery stenosis of $\geq$ 50% based on CTCA. Of the 10 studies, 6 studies involved the use of CTCA on asymptomatic subjects with higher cardiac risks, including 5 prospective observational studies and 1 retrospective observational study. Subjects in these studies either: 1) had established cardiovascular risk factors such as diabetes mellitus, obesity, or stroke (Messerli et al.,[15] Dedic et al.,[5] Nadjiri et al.,[17] Hur et al.,[11] and Park et al.[19]); 2) were determined to have high cardiac risks using validated cardiovascular risk calculators (Dedic et al.); or 3) were determined by the attending cardiologists to have elevated cardiovascular risk profiles (Hadamitzky et al.[8]). The characteristics of the included studies are shown in **Table I**.

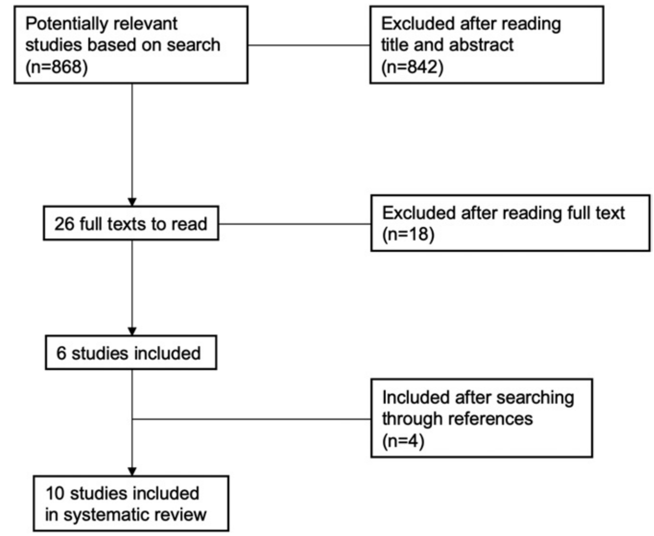

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses flow chart of the search process.

In general, the studies showed higher event rate or risk of cardiac events as the extent of coronary obstruction increased (**Table II**). When compared to subjects with no or nonobstructive CAD, those with obstructive CAD on CTCA had hazard ratios (HR) for cardiac events ranging from 1.42 to 105.48.[3,5,8,11,13] When compared to subjects with no or nonobstructive CAD, those with 3-vessel, 2-vessel, and 1-vessel obstructions on CTCA had HR for cardiac events ranging from 2.91 to 42.7, 2.20 to 21.7, and 1.42 to 19.9, respectively.[3,5,11] Lastly, when compared to subjects without CAD on CTCA, Cho et al.[3] found that subjects with nonobstructive CAD had an HR of 1.19 for cardiac events.

Cho et al.'s study, which involved 7590 subjects, is the largest study found in the current review. The study obtained results from the CONFIRM registry (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry), an open-label, 12-center, 6-country observational registry of 27,125 consecutive patients. This study reported an HR of 1.19 (P = 0.511, 95% CI: 0.71 to 1.98) for cardiac events in subjects found to have nonobstructive CAD as compared to those without CAD on CTCA. The HR of subjects with 1-, 2-, and 3-vessel obstructions as compared to those without CAD on CTCA were 1.42 (P = 0.23, 95% CI: 0.80 to 2.53), 2.20 (P = 0.013, 95% CI: 1.19 to 4.16), and 2.91 (P = 0.001, 95% CI: 1.55 to 5.47), respectively.

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Table I. Study Characteristics.

AUTHOR	PUBLICATION YEAR	DESIGN	STUDY SIZE	KEY CHARACTERISTIC OF SUBJECTS	AGE*	GENDER	FOLLOW-UP DURATION (MONTHS)	EVENTS MEASURED
Messerli et al.[15]	2017	Prospective	54	Obese	48.5	43% male	73.2	MACE
Dedic et al.[5]	2016	Prospective	665	High cardiac risk	56	62.7% male	36	All-cause mortality; nonfatal MI; unstable angina; revascularization
Nadjiri et al.[17]	2016	Prospective	1487	DM	58.1	69.5% male	66.1	MACE
Hur et al.[11]	2015	Prospective	914	Stroke	64	68.5% male	13.6	MACE
Park et al.[19]	2014	Prospective	557	DM	62.4	59.4% male	33.7	Cardiac death; nonfatal MI; ACS; revascularization
Cho et al.[3]	2012	Retrospective	7590	--	58	61% male	24	All-cause mortality; nonfatal MI
Jin et al.[13]	2012	Retrospective	914	--	40.4	60.4% male	26.8	Cardiac death; nonfatal MI; unstable angina; revascularization
Cassagneau et al.[2]	2012	Prospective	52	Awaiting liver transplant	52.9	76% male	17.8	Cardiac death; nonfatal MI; revascularization; CHF; serious arrhythmia
Hadamitzky et al.[8]	2010	Retrospective	451	High cardiac risk	58.6	74% male	27.5	Cardiac death; nonfatal MI; unstable angina; revascularization
Choi et al.[4]	2008	Prospective	1000	--	50	63% male	17	Cardiac death; nonfatal MI; unstable angina; revascularization

* All studies used mean age.
DM: diabetes mellitus; MI: myocardial infarction; ACS: acute coronary syndrome; MACE: major adverse cardiovascular events; CHF: congestive heart failure.

The reported annual event rates of subjects with nonobstructive or no CAD on CTCA were extremely low, ranging from 0 to 0.5%.[4,8,19] Messerli et al.'s[15] study found that CTCA had an negative predictive value (NPV) of 100% (95% CI: 90.1–100%) for MACE in obese subjects with no CAD on CTCA. Cassagneau et al.'s[2] results were similar, and showed that CTCA had an NPV of 95% (95% CI: 0.82 to 0.99) in subjects found to have nonobstructive or no CAD on CTCA. In contrast, those with obstructive CAD on CTCA had annual event rates ranging from 2.5 to 7.1%.[8,19] Park et al.'s[19] study also reported a lower 3-yr survival of 90.9% ($P < 0.001$) for subjects with obstructive CAD as compared to 99.2% for subjects with nonobstructive or no CAD.

DISCUSSION

Our review summarized the prognostic value of CTCA in asymptomatic subjects among the general population. Compared to subjects without CAD or with nonobstructive CAD, subjects with obstructive CAD had higher absolute (2.5–7.1%) and relative risks (HR = 1.42 to 105.48) of cardiac events. The risks of cardiac events rose with the total number of coronary vessels occluded on CTCA, and subjects with 3-vessel obstructions had the highest risks of cardiac events.

Our review also found that subjects with nonobstructive CAD on CTCA had a higher risk of cardiac events as compared to those without (HR 1.19, $P = 0.511$), suggesting that subjects with nonobstructive CAD on CTCA did not have the same prognosis as those without CAD. However, as this result was not statistically significant, further research will need to be carried out to validate this finding.

An important finding from our review was that subjects with no CAD on CTCA had an extremely low rate of cardiac event (annual event rate of 0–0.5%). Messerli et al.'s[15] study found that over a mean follow-up period of 6.1 yr, a normal CTCA had a high NPV of 100% (95% CI: 90.1–100%) for cardiac events. With a high NPV, CTCA can be an invaluable tool in excluding patients with coronary artery disease.

The findings of this systematic review are relevant to modern military and civilian aeromedical licensing authorities that accept the use of CTCA as part of their cardiovascular risk assessment process, with the increasing adoption of CTCA in screening for clinically silent CAD, or as second line investigation when standard treadmill exercise tests return as abnormal or equivocal. Incorporating CTCA findings as part of the aeromedical decision-making process can be challenging, as opposed to standard clinical care of CAD patients, as the aeromedical risk evaluation of aircrew is anchored on occupational considerations with stricter requirements. As such, any proposed protocol for cardiovascular risk assessment using CTCA would have to balance the cardiac risks determined by CTCA and the acceptable occupational risk thresholds in the aviation environment.[6] In this regard, the aeromedical standards for military flying, especially for single-seat fast jet pilots, may need to be stricter due to the inherent higher occupational risks.

In the Republic of Singapore Air Force (RSAF), the first indication of a possible underlying CAD in an asymptomatic aircrew is through an abnormal stress ECG performed during their annual medical examinations. Aircrew with abnormal stress ECG will need to undergo functional cardiac imaging (e.g., stress echocardiography or myocardial perfusion imaging) to

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Table II. Summary of Study Outcomes by Hazard Ratio/Relative Risk.

AUTHOR	OUTCOME
Dedic et al.[5]	HR (Compared to subjects with No CAD) 3-vessel obstruction: 26.12 ($P < 0.001$) 2-vessel obstruction: 14.54 ($P < 0.001$) 1-vessel obstruction: 5.09 ($P = 0.04$) Obstructive CAD: 11.23 ($P = 0.001$) No CAD: 1.0
Nadjiri et al.[17]	HR (Compared to subjects with No CAD) Obstructive CAD: 2.0 in DM cases (95% CI: 0.5 to 7.8), 1.9 in non- DM cases (95% CI: 1.1 to 3.4) NCP: 1.2 (95% CI: 0.9 to 1.6) No CAD: 1.0
Hur et al.[11]	HR (Compared to subjects with No CAD) 3-vessel obstruction: 42.7 ($P < 0.001$, 95% CI: 5.47 to 333.83) 2-vessel obstruction: 21.7 ($P = 0.005$, 95% CI: 2.43 to 194.93) 1-vessel obstruction: 19.9 ($P = 0.004$, 95% CI: 2.52 to 157.14) Obstructive CAD: 26.5 ($P = 0.001$, 95% CI: 3.58 to 196.41) Non-obstructive/No CAD: 1.0
Cho et al.[3]	HR (Compared to subjects with No CAD) 3-vessel obstruction: 2.91 ($P = 0.001$, 95% CI: 1.55 to 5.47) 2-vessel obstruction: 2.20 ($P = 0.013$, 95% CI: 1.19 to 4.16) 1-vessel obstruction: 1.42 ($P = 0.23$, 95% CI: 0.80 to 2.53) Non-obstructive CAD: 1.19 ($P = 0.511$, 95% CI: 0.71 to 1.98) No CAD: 1.0
Jin et al.[13]	HR (Compared to subjects with No CAD) Obstructive CAD: 105.48 ($P = 0.001$) NCP: 49.17 ($P = 0.002$) No CAD: 1.0
Hadamitzky et al.[8]	RR (Compared to subjects with No CAD) Obstructive CAD: 13.9 (95% CI 4.0 to 48.0) Non-obstructive/No CAD: 1.0

HR: hazard ratio; RR: relative risk; CAD: coronary artery disease; DM: diabetes mellitus; CI: confidence interval; NCP: noncalcified plaques.

exclude the presence of cardiac ischemia resulting from underlying CAD. Aircrew with a positive functional cardiac imaging test will be referred to a cardiologist for further workup. Remaining aircrew with a negative functional cardiac imaging and who are above the age of 40 are required to undergo coronary artery calcium scoring (CACS) to determine the presence of underlying CAD. Current evidence does not support the use of CACS in patients less than 40 yr of age.[9]

As part of the existing RSAF protocol, aircrew with CACS of 10 or less and who have normal cardiovascular risk profiles can be returned to flight related duties, while those with calcium scores of 400 or more will be restricted from all military flying duties permanently. Studies have shown that a CACS of 400 or more is an independent predictor of cardiac events.[1,24] Following our review, any aircrew with an intermediate calcium score (i.e., CACS 11–399) or those with higher cardiovascular risk profiles (i.e., diabetes mellitus, smoking, obesity, hypertension, or first-degree family history of premature CAD) in spite of a low calcium score (i.e., CACS < 10) will have the CTCA performed as part of the RSAF cardiac screening protocol.[17,19] **Fig. 2** illustrates the revised cardiac screening protocol for asymptomatic CAD in military pilots and aircrew.

Aircrew found to have absent or minimal CAD (i.e., ≤ 25% stenosis) in a non-left main coronary artery on CTCA can be returned to flight related duties. All other CTCA results should be further evaluated with an invasive angiogram. We had chosen these risk thresholds as the physiological demands of military flying are inherently higher than that in the civilian context. Due to its poorer temporal resolution, the accuracy of CTCA in determining the severity of a coronary artery lesion can vary up to ± 25% in comparison to that of an invasive angiogram.[14] As such, the final aeromedical disposition should be decided based on the findings of the invasive angiogram.

Our pathway differs from the recommendations on CTCA published by the NATO Aviation Working Group.[7] While CTCA was proposed by the Working Group to be used in aircrew with elevated cardiac risks, they had recommended that aircrew with single or aggregate stenoses on CTCA of < 50% or left main stenosis of < 30% to be returned to unrestricted flying duties. However, having reviewed the existing studies, we believe that the risk of cardiac events in military aircrew with nonobstructive CAD is not equivalent to those without CAD. Therefore, we have further stratified the CTCA to accept only aircrew with non-left main stenoses of ≤ 25%. This is equivalent to the Society of Cardiovascular Computed Tomography (SCCT)'s category of "minimal stenosis".[14] Apart from the NATO Aviation Working Group, we are not aware of any other recommendations on the interpretation of CTCA results issued by aeromedical licensing authorities.

We acknowledge the inherent limitations of our systematic review. Of note, the subjects across the included studies were heterogeneous in nature; while each study only employed asymptomatic subjects, the inclusion criteria were varied across the studies. Second, while the results of the study have been used to inform the development of a pathway to assess the cardiovascular risk of our aircrew, there are key demographic differences between the study populations (mean age of included studies = 56 yr) and our younger aircrew population (< 50 yr old). Consequently, the proposed protocol would likely overestimate the aircrew's cardiac risks, as most of the studies included patients at significantly higher risks compared to the lower risk profile and younger aircrew demographic. Such an approach allows the proposed pathway to have a higher sensitivity and avoid according fit-to-fly statuses to military aircrew who may subsequently develop cardiac events. However, this may be done at the expense of additional invasive investigations and may result in higher than expected flying restrictions among military pilots and aircrew.

To our knowledge, this is the first systematic review that focused on the outcomes of CTCA in asymptomatic subjects of higher and normal cardiac risks, with the results then directly applied to develop a pathway to guide the aeromedical fitness assessment of military aviators with asymptomatic CAD. It is envisaged that the pathway may be applied to other occupational groups that undertake safety-critical tasks, such as airline transport pilots, train operators, and heavy vehicle drivers. With more evidence on the use of CTCA in future studies, it is hoped that the cardiac protocol can be further updated to better inform on the risks of military flying.

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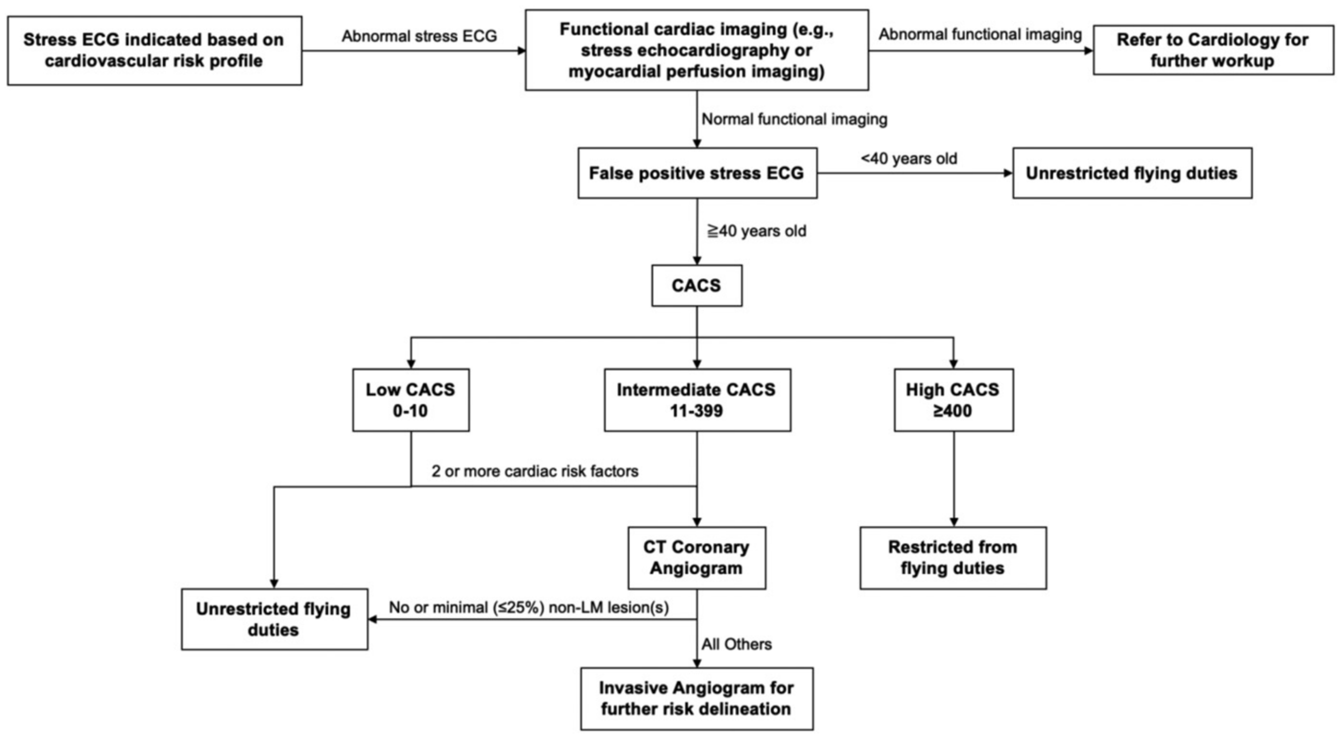

Fig. 2. Proposed aeromedical disposition pathway for military aviators with asymptomatic coronary artery disease.

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