Cardiovascular Risk Factor Modification in Asymptomatic Adults and Implications for Pilots

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Abstract: This study aims to examine the available evidence that supports a more aggressive approach to managing asymptomatic people with low to intermediate cardiovascular risks; to evaluate the appropriate threshold for initiating pharmacologic interventions to treat hyperglycaemia, hyperlipidaemia, and hypertension; and to describe the implications for airline pilots. A systematic search was performed employing an OvidSP interface, including all EBM Reviews, EMBASE, and Ovid MEDLINE databases. Data, including sixteen randomised controlled trials, on the appropriate threshold for initiating pharmacologic interventions were extracted. Studies on the treatment of hyperlipidaemia indicated that the threshold for initiation of intervention in intermediate-risk people is a LDL-C level of 3.36 mmol/l (130 mg/dl). There was no lower limit or optimal LDL-C level below which further reduction was no longer beneficial. Studies on the treatment of hyperglycaemia suggested that a threshold of fasting plasma glucose of ≥5.3 mmol/l (95 mg/dl) and 2-hour postprandial glucose level of 7.8 mmol/l (140 mg/dl) is reasonable for initiating pharmacologic intervention. Initiating treatment to people with a blood pressure of ≥130/≤89 mmHg or ≤139/≥85 mmHg significantly reduced the risk of developing stage 1 hypertension. Multifactorial intervention studies showed that, in hypertensive patients (BP ≥160/≥100 mmHg), initiating treatment to those with a total cholesterol of 6.5 mmol/l (251.35 mg/dl) or higher resulted in a significant reduction in the risk of developing fatal and non-fatal cardiovascular events. The available evidence from large quality trials supports a more aggressive approach to managing hyperglycaemia, hyperlipidaemia, and hypertension in asymptomatic pilots with a 5-year CVD risk of 5–10% and 10–15%.

Keywords: cardiovascular risk, airline pilot, asymptomatic population, risk reduction.

Introduction

Risk factor modification is an important component in the cardiovascular risk assessment of airline pilots, especially among those with intermediate-high risk without proven significant disease [1, 2]. Preventive measures have focused on the main risk factors involved in the calculation of cardiovascular disease (CVD) risk score, such as hyperlipidaemia, hypertension, hyperglycaemia, and smoking history. A study examining cardiovascular risk factors in a commercial flight aircrew found significantly higher incidences of...
increased systolic blood pressure and hyperlipidaemia in pilots when compared with the general population [3, 4]. As airline pilots are required to have a high standard of cardiovascular health to continue their employment and to prevent sudden cardiovascular events that could jeopardise flight safety, a more aggressive risk modification approach is often practised in aviation medicine settings [5, 6]. This is supported by a finding from a New Zealand study that airline pilots had a higher prevalence of medicated hyperlipidaemia compared to the general population (13.8% vs 7.9%; P-value: <0.01) [7]; whether this is due to a greater prevalence of hyperlipidaemia or an increased likelihood of this being detected and treated is not stated.

It remains unclear however, whether such an approach is consistent with current cardiovascular management guidelines, and whether currently available scientific evidence supports those practices. Of particular interest is the availability of a more appropriate cardiovascular risk factor threshold in initiating pharmacologic interventions. The present study seeks to prove that a more aggressive approach to the management of the increased individual cardiovascular risk factors in the airline pilot population would be reasonable.

Most of the current cardiovascular management guidelines are designed to support strategies to address increases in the levels of risk factors. A summary of recommendations from the New Zealand Guideline Group (NZGG) published in the New Zealand Primary Care Handbook suggested that all treatment decisions should be based on a patient’s 5-year absolute cardiovascular risk as calculated by the NZGG cardiovascular risk chart [8, 9], instead of making a decision based on individual risk factor levels. The overall goal is that, among people with a 5-year cardiovascular risk of more than 15%, the treatment should be aimed at lowering cardiovascular risk. There is no ideal lipid level suggested as a threshold. A total cholesterol of about 4–8 mmol/l in people without known CVD should be interpreted in the context of their cardiovascular risk. Likewise for hypertension management, it is stated that, in asymptomatic people with a blood pressure (BP) level between 115/70 and 170/100 mmHg, decisions to initiate therapy should be based on the individual’s cardiovascular risk.

This study presents a systematic review that aims to critically examine the available evidence that supports a more aggressive approach to managing intermediate-risk asymptomatic people, to evaluate the appropriate threshold for initiating pharmacologic interventions to treat hyperglycaemia, hyperlipidaemia, and hypertension in asymptomatic people with low to intermediate CVD risks, and to describe how the findings can be applied to the CVD risk management of the airline pilot population.

**Methods**

**Data sources and searches**

A systematic literature review was performed employing the database search platform of OvidSP (http://ovidsp.tx.ovid.com) in July 2019. A summary of the search strategy is presented in Table 1. The databases and resources used for this review were all Evidence Based Medicine (EBM) Reviews, EMBASE – all years (1947-present with daily update), and Ovid MEDLINE(R) (1946 to present with daily updates).

**Inclusion and exclusion criteria**

The inclusion criteria for this review included trials that examined risk factor modification using pharmacologic intervention for conditions such as hyperglycaemia, hyperlipidaemia, hypertension, or multiple CVD risks; trials that involved asymptomatic people or patients without known cardiovascular disease; and randomised controlled trials.

The exclusion criteria for this review included studies that involved only symptomatic people or patients with established cardiovascular diseases, studies that did not examine the risk factors threshold, studies that only assessed efficacy of a new drug or a new marker, and studies which were not published in English.

**Risk of bias assessment**

The bias risk of trials was evaluated by employing the components recommended by the Cochrane Collaboration [10], including random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data addressed (attrition bias); and selective reporting (reporting bias).
Trials with a high or unclear risk for bias for any one of the above components were considered trials with a high risk of bias. Otherwise, they were regarded as trials with a low risk of bias.

Results

The initial search retrieved 945 potentially relevant articles. After scanning the titles and abstracts, 776 articles were excluded. Consequently, the full text of 169 articles were reviewed, which resulted in the exclusion of 153 studies. Finally, 16 randomised controlled trials relevant to the study aims were included. A flowchart of the selection of citations is shown in Fig. 1.

The 16 randomised controlled trials came from 13 major studies. The characteristics, risk of bias assessment and sources of funding for the included studies can be seen in Table 2. Most of the studies are considered as having a low risk of bias. Two studies, the TOGETHER and the CUSP trials, had insufficient reporting of attrition or exclusions that allowed appreciation of attrition bias. The trials were then grouped into three main categories including studies focusing on interventions to hyperlipidaemia, hyperglycaemia, hypertension, and multiple cardiovascular risk factors. There were no studies found on risk factor modification based on coronary artery calcium scores.

Studies on hyperlipidaemia

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AF/TexCAPS) was the first primary prevention trials of statin performed in asymptomatic middle-aged adults with low to moderate risk for CVD [11]. This study examined the associations between reduction
of low density lipoprotein cholesterol (LDL-C) and first acute major coronary events in a cohort of apparently healthy middle-aged men, women, and older people with average total cholesterol (TC), average LDL-C levels, and below-average high-density lipoprotein cholesterol (HDL-C) levels. The main finding showed that treatment with lovastatin significantly reduced the relative risk of the first Acute Major Coronary Events (AMECs) by 37%, with a 25% reduction in LDL-C and a 6% increase in HDL-C. The author suggested that treatment with lovastatin could be considered in asymptomatic people at low-moderate risk for CVD with LDL-C levels >3.36 mmol/l (>130 mg/dl) and HDL-C levels <1.29 mmol/l (<50 mg/dl).

A further post-hoc analysis of this trial specifically evaluated the associations between the 1-year changes in HDL-C and LDL-C with lovastatin and subsequent acute major coronary events [12]. The main findings indicated that patients with LDL-C of <115 mg/dl and an increase in HDL-C of ≥7.5% at year 1 had the lowest acute major coronary event rate (9 events per 2,544 person-years, or 3.53 per 1,000 person-years).
Likewise, patients with both an increase in HDL-C of ≥7.5% and a decrease in LDL-C of >25%, and patients with both an absolute HDL-C of ≥3.5 mg/dl and LDL-C <115 mg/dl at year 1, had an event rate of 4.11 and 4.34 per 1,000 person-years, respectively.

The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial examined the impact of achieving LDL-C levels <50 mg/dl (<1.29 mmol/l) with rosuvastatin on cardiovascular and adverse events in adults without known CVD [13]. The main findings indicated that participants in the intervention group who attained LDL-C <50 mg/dl had a lower risk of CVD events. For the whole study cohort, rosuvastatin was found to reduce major CVD events by 44% compared with placebo, and among participants achieving LDL-C <50 mg/dl, the major cardiovascular events were reduced by 65%.

The Management of Elevated cholesterol in the primary prevention Group of Adult Japanese (MEGA) study assessed the association between reduction in LDL-C and the decrease in cardiovascular disease in Japanese patients with mild to moderate hypercholesterolemia [14]. The principal findings indicated that there was a significant 33% reduction in the primary endpoint in the intervention group compared with the control group. Additionally, the mean LDL-C was reduced by 18% in the intervention group compared with 3.2% in the control group.

In another report of this trial, the author divided the subjects into those with LDL-C levels <150, 150-165, and >165 mg/dl; and suggested that, regardless of the severity of hypercholesterolemia, pravastatin may be beneficial in patients with LDL-C ≥150 mg/dl (3.88 mmol/l) [15].

A further post-hoc analysis of this trial examined patients in the intervention arm who were divided into tertiles by their on-treatment LDL-C level, and additionally into quintiles by their on-treatment LDL-C level and LDL-C reduction rate from baseline [16]. The main findings showed that in this low risk Japanese patient population, a usual dose (10–20 mg) of pravastatin therapy was adequate to decrease cardiovascular risk, with an achieved LDL-C level of <133.4 mg/dl. No further CVD risk reduction was found below an achieved LDL-C of 120.8 mg/dl. There was a significant risk reduction found in the group with a 20–30% LDL-C decrease.

The West of Scotland Coronary Prevention Study (WOSCOPS) determined whether pravastatin prevents coronary events in asymptomatic men with moderate hypercholesterolemia [17]. The main findings showed that treatment with pravastatin significantly reduced the relative risk of nonfatal myocardial infarction (MI) and death from coronary heart disease (CHD) by 31%, with a 26% reduction in LDL-C and a 20% reduction in plasma cholesterol levels.

The Heart Outcomes Prevention Evaluation (HOPE)-3 trial examined the benefits of statins among intermediate-risk ethnically diverse people without CVD [18]. The main finding indicated that treatment with rosuvastatin at a dose of 10 mg per day for a period of 5.6 years resulted in a significantly lower risk of cardiovascular events than that with placebo (relative risk reduction of 24%).

The Studies of PCSK9 Inhibition and the Reduction of Vascular Events (SPIRE) assessed the efficacy of bococizumab in patients at high cardiovascular risk [19]. The SPIRE studies consisted of 2 randomised, placebo-controlled trials, of which 15.5% were asymptomatic people (high-risk primary prevention category). The principal findings showed that bococizumab had no benefit among lower-risk patients but did have a significant benefit in a trial involving higher-risk patients with LDL-C ≥2.6 mmol/l (relative risk reduction of 12.0%).

Studies on hyperglycaemia

The Diabetes Prevention Program (DPP) study investigated whether intensive lifestyle modification or pharmacologic treatment of pre-diabetes prevents or postpones the development of subsequent type 2 diabetes [20]. The principal findings showed that, compared with placebo, the intensive lifestyle intervention reduced the incidence of diabetes by 58% and of metformin by 31%.

The Diabetes Prevention Program Outcomes Study (DPPOS) was a follow-up study to the DPP that investigated diabetes risk reduction among people who had reversed to normal glucose regulation versus those who remained with pre-diabetes during the DPP study [21]. The main findings showed a 56% reduction in diabetes incidence in the participants who had returned to a normal glucose level.
The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) randomised trial aimed to evaluate the effect of acarbose in postponing or preventing conversion of impaired glucose tolerance to type 2 diabetes mellitus [22]. The main findings showed that there was a significant 25% reduction in the risk of progression to diabetes in the intervention group.

Studies on hypertension

The Trial of Preventing Hypertension (TROPHY) study examined whether early pharmacologic treatment of prehypertension can prevent or delay the development of subsequent stage 1 hypertension [23]. The principal findings indicated significant 66.3% and 15.6% risk reductions in the treatment group after two years and four years, respectively. Overall, the risk reduction of developing stage 1 hypertension over the 4-year study period in the treatment group was 42%.

Studies on multifactorial intervention

The simultaneous treatment to attain BP and lipid goals and reduced CV risk burden (TOGETHER) trial examined whether a multiple risk factor management strategy would result in better BP or lipid control compared with usual approaches to BP intervention [24]. The main findings were that 67.8% participants in the intervention group attained the combined BP and LDL-C goals, compared with 9.6% in the control group (risk reduction was 58.2%).

The Caduet in Untreated Subjects Population (CUSP) trial assessed the efficacy/safety of a combined drug in patients with hypertension and dyslipidaemia [25]. The main results showed that 47.6% of participants in the intervention group attained the combined BP and LDL-C goals, compared with 1.7% in the control group, at week 4. Further improvements were found at week 8, when the achievement of the goals was larger in the intervention group than in the control group (55.6% vs 5.0%, respectively). This resulted in a 50.6% risk reduction.

The aim of the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA) was to examine associations between cholesterol lowering and reductions in major cardiovascular events in hypertensive patients who are not conventionally considered dyslipidaemic [26]. The principal findings demonstrated that, in hypertensive patients, cholesterol lowering therapy reduced the incidence of non-fatal MI and fatal CHD by 36%, compared with those treated by an antihypertensive only.

Summary of the results

A summary of the results can be seen in Table 3, and the point estimate and its confidence interval for the included studies are shown in Fig. 2. Table 3 summarises the included studies, the principal findings, and other important results related to the aims of the present study. The main findings from studies focusing on the treatment of hyperlipidaemia indicated that the threshold suggested for initiation of a more aggressive pharmacologic intervention is a LDL-C level of 3.36 mmol/l (130 mg/dl) or higher. There is no lower limit and no optimal LDL-C level below which further reduction is no longer beneficial. Studies that focused on treatment of hyperglycaemia suggested that pharmacologic intervention to pre-diabetes would result in a significant reduction in the risk of developing type-2 diabetes. This means that a threshold of fasting plasma glucose of ≥5.3 mmol/l (95 mg/dl) or higher, and a 2-hour postprandial glucose level of 7.8 mmol/l (140 mg/dl) or greater, would be reasonable for initiating pharmacologic intervention.

A study focusing on intervention of prehypertension revealed that initiating treatment to people with a BP of ≥130/≤89 mmHg or ≤139/≥85 mmHg significantly reduced the risk of developing stage 1 hypertension, which is one of the major CVD risk factors.

A large study on multifactorial intervention (the ASCOT-LLA trial) showed that, in hypertensive patients (BP ≥160/≥100 mmHg), initiating treatment to those with a total cholesterol level of 6.5 mmol/l (251.35 mg/dl) or higher resulted in a significant reduction of the risk of developing fatal and non-fatal cardiovascular events.

Figure 2 illustrates the point estimates of each study with its confidence interval. The 95% confidence intervals (CIs) of all the included studies, except the SPIRE, do not overlap with the value 1. In other words, intervention is better, as all the point estimates and their 95% CIs are to the left of the line of no effect.

Among the studies focusing on interventions to hyperlipidaemia, the JUPITER trial showed the most significant relative reduction of risk in CVD events with
the narrowest 95% CI. Similarly, among the studies on hyperglycaemia, the DPPOS trial demonstrated the most significant relative reduction of risk in development of diabetes with the narrowest 95% CI.

**Discussion**

All the studies included in the present review favoured intervention or a more aggressive approach to hyperlipidaemia compared with that suggested by the cardiovascular management guidelines. However, there are some drawbacks that might have influenced the results of the trials that should be considered before drawing a conclusion.

The JUPITER trial demonstrated the most significant CVD risk reduction. The main limitation of this study is related to the application of post-hoc analysis, where the classification into 2 rosuvastatin groups was based on a non-randomised outcome, and it was based on a population with elevated high sensitive C-reactive protein (hs-CRP). In the search for a cut-off below which further LDL-C lowering no longer reduces CVD events, this study proved that the lowest threshold or percent reduction for cardiovascular prevention would be <50 mg/dl (1.29 mmol/l) or >50% LDL-C reduction. However, another rigorous study, the HOPE-3 trial, proved that there should be no lower limit. Low dose statins have been proven to be beneficial in reducing the risk of cardiovascular events among intermediate-risk asymptomatic people with a normal range of LDL-C. The AF/TexCAPS study suggested that the threshold for initiating pharmacologic intervention was a LDL-C >3.36 mmol/l. The MEGA study suggested a slightly higher threshold level for initiating drug therapy, which was a LDL-C of 3.88 mmol/l or greater. Similar to the AF/TexCAPS study, the CVD risk reduction that could be obtained by more aggressive LDL-C reduction remains unclear.

**Fig. 2. Summary of point estimate of the studies.** AF/TexCAPS: The Air Force/Texas Coronary Atherosclerosis Prevention Study, JUPITER: The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, MEGA: The Management of Elevated cholesterol in the primary prevention Group of Adult Japanese study, WOSCOPS: The West of Scotland Coronary Prevention Study, HOPE-3: The Heart Outcomes Prevention Evaluation –3 trial, SPIRE: The Studies of PCSK9 Inhibition and the Reduction of Vascular Events, DPP: The Diabetes Prevention Program study, DPPOS: The Diabetes Prevention Program Outcomes Study, STOP-NIDDM: The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus, TROPHY: The Trial of Preventing Hypertension study, ASCOT-LLA: The aim of the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm.
Table 3. Summary of the principal findings including suggested threshold for pharmacologic therapy and optimal level

| Study                          | Sample (n) | Comparison | Follow-up | Primary Endpoint | Risk Reduction | Point Estimate (95% CI) | Suggested Threshold (Optimal Level)* |
|--------------------------------|------------|------------|-----------|------------------|----------------|--------------------------|---------------------------------------|
| **Studies on Hyperlipidaemia** |            |            |           |                  |                |                          |                                       |
| AF/TexCAPS                    | 6,605      | Diet and Lovastatin vs Diet and Placebo | 5.2 years | MI, sudden cardiac death and unstable angina | 37.0%          | RR: 0.63 (0.50–0.79)     | LDL-C >3.36 mmol/l                    |
| JUPITER                       | 17,802     | Rosuvastatin vs Placebo                  | 2 years   | Cardiovascular death, MI, stroke, revascularisation, unstable angina | 44.0%          | HR: 0.56 (0.46–0.69)     | LDL-C ≥ 3.36 mmol/l                  |
| MEGA                          | 7,832      | Diet and Pravastatin vs Diet alone       | 5.3 years | MI, sudden cardiac death, revascularisation and angina | 33.0%          | HR: 0.67 (0.49–0.91)     | LDL-C ≥ 3.88 mmol/l (<3.1 mmol/l)    |
| WOSCOPS                       | 6,595      | Pravastatin vs Placebo                   | 4.9 years | Nonfatal MI and death from coronary heart disease | 31.0%          | RR: 0.69 (0.57–0.83)     | LDL-C ≥ 4.5 mmol/l                   |
| HOPE-3                        | 12,705     | Rosuvastatin vs Placebo                  | 5.6 years | Cardiovascular death, MI, stroke, revascularisation, heart failure, cardiac arrest | 24.0%          | HR: 0.76 (0.64–0.91)     | No lower limit for LDL-C             |
| SPIRE                         | 27,438     | Bococizumab vs Placebo                   | 10 months | Cardiovascular death, MI, stroke, revascularisation, unstable angina | 12.0%          | HR: 0.88 (0.76–1.02)     | LDL-C ≥ 2.6 mmol/l in high-risk people |
| **Studies on Hyperglycaemia**  |            |            |           |                  |                |                          |                                       |
| DPP                           | 3,234      | Lifestyle and Metformin vs Lifestyle and Placebo | 2.8 years | Type 2 diabetes | 31.0%          | HR: 0.69 (0.57–0.83)     | FPG ≥ 5.3 mmol/l                     |
| DPPOS                         | 1,990      | Pre-diabetes vs Normal glucose level     | 5.4 years | Type 2 diabetes | 56.0%          | HR: 0.44 (0.37–0.55)     | FPG ≥ 5.3 mmol/l                     |
| STOP-NIDDM                    | 1,368      | Acarbose vs Placebo                      | 3.3 years | Type 2 diabetes | 25.0%          | HR: 0.75 (0.63–0.90)     | 2-h pp ≥ 7.8 mmol/l                  |
| **Studies on Hypertension**   |            |            |           |                  |                |                          |                                       |
| TROPHY                        | 772        | Candesartan for 2 years vs Placebo       | 4 years   | Stage 1 hypertension | 42.0%          | RR: 0.58 (0.49–0.70)     | BP: ≥ 130/ ≤ 89 mmHg or ≤ 139/ ≥ 85 mmHg |
| **Studies on Multifactorial Intervention** | | | | | | | |
| TOGETHER                      | 218        | Amlodipine/Atorvastatin vs Amlodipine    | 6 weeks   | BP <140/90 mmHg and LDL-C <2.59 mmol/l | 58.2%          | OR: 19.0 (9.1–39.6)     | BP: ≥ 159/ ≥ 99 mmHg and LDL-C ≥ 2.59 mmol/l |
| CUSP                          | 130        | Amlodipine/Atorvastatin vs Placebo       | 8 weeks   | BP <140/90 mmHg and LDL-C <2.59 mmol/l | 50.6%          | OR: 23.8 (6.7–85.0)     | BP: ≥ 140/ ≥ 90 mmHg and LDL-C ≥ 2.59 mmol/l |
| ASCOT-LLA                     | 10,305     | Antihypertensive and Atorvastatin vs Antihypertensive and Placebo | 3.3 years | non-fatal MI and fatal coronary heart disease | 36.0%          | HR: 0.64 (0.50–0.83)     | BP: ≥ 160/ ≥ 100 mmHg and TC: ≥ 6.5 mmol/l |

*Threshold suggested for initiation of more aggressive pharmacologic intervention and optimal level below which further reduction no longer beneficial. RR: Relative Risk, HR: Hazard Ratio, OR: Odds Ratio, MI: myocardial infarction, LDL-C: low density lipoprotein cholesterol, HDL-C: high density lipoprotein cholesterol, FPG: fasting plasma glucose, 2-h pp: 2-hour postprandial glucose levels, BP: blood pressure, TC: total cholesterol. AF/TexCAPS: The Air Force/Texas Coronary Atherosclerosis Prevention Study, JUPITER: The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, MEGA: The Management of Elevated cholesterol in the primary prevention Group of Adult Japanese study, WOSCOPS: The West of Scotland Coronary Prevention Study, HOPE-3: The Heart Outcomes Prevention Evaluation –3 trial, SPIRE: The Studies of PCSK9 Inhibition and the Reduction of Vascular Events, DPP: The Diabetes Prevention Program study, DPPOS: The Diabetes Prevention Program Outcomes Study, STOP-NIDDM: The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus, TROPHY: The Trial of Preventing Hypertension study, TOGETHER: The simultaneous treatment to attain blood pressure and lipid goals and reduced CV risk burden trial, CUSP: The Caduet in Untreated Subjects Population trial, ASCOT-LLA: The aim of the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm.
because of the small number of patients who achieved LDL-C of <100 mg/dl as well as LDL-C reduction of >30% in the 5-year follow-up. However, the findings supported the current Japan Atherosclerosis Society guidelines that for primary prevention in patients with some risks for CVD, the LDL-C target of 120–140 mg/dl (3.10–3.62 mmol/l) is reasonable [27].

The WOSCOPS study provides justification for reducing cholesterol levels in asymptomatic subjects with moderate hypercholesterolemia. Treating asymptomatic patients with LDL-C levels of 174 to 232 mg/dl (4.5–6.0 mmol/l) was proven to significantly reduce the incidence of MI and death from CHD. In the absence of a recommendation for a threshold level for initiating drug therapy in asymptomatic people with low to intermediate cardiovascular risk, the LDL-C level of 4.5 mmol/l or higher seems to be reasonable.

A large meta-analysis of clinical trials of statins conducted by the Cholesterol Treatment Trialists’ (CTT) Collaborators supported the above findings [28]. This study found that in people with a 5-year risk of major CVD events of less than 10%, each 1 mmol/l reduction in LDL cholesterol resulted in an absolute reduction in major CVD events of about 11 per 1,000 over 5 years. This benefit largely exceeded any recognised hazards of statin therapy. This was supported by a large recent meta-analysis of the efficacy and safety of statin therapy which concluded that, in primary prevention, the benefits of statins largely outweigh the possible side effects [29].

There is no clear cholesterol goal or end point for initiating therapy in the NZGG guidelines for asymptomatic people with a 5-year CVD risk of <15%. However, in the Adult Treatment Panel (ATP) III guidelines, it is recommended that for people with 2 or more risk factors or with 10-year risk of 10–20% by Framingham risk scoring, the goal for LDL-C is <130 mg/dl (3.36 mmol/l) [30]. In the American Heart Association (AHA) 2018 guideline on the management of blood cholesterol, it is stated that the more LDL-C is reduced by statin therapy, the greater will be the subsequent risk reduction; and the guideline suggests the use of a maximally tolerated statin to lower LDL-C levels by ≥50%. This guideline recommends that the decision to start statin therapy should be based on individual absolute risk, risk-enhancing factors, and age groups [31].

In the 2019 American College of Cardiology/American Heart Association (ACC/AHA) Guideline on the Primary Prevention of Cardiovascular Disease, the writing committee agrees that for young adults (20 to 39 years of age), priority should be given to estimating lifetime risk and promoting a healthy lifestyle. Drug therapy is indicated only in select patients with moderately high LDL-C (≥160 mg/dl) or those with very high LDL-C (≥190 mg/dl). In adults 40 to 75 years of age, 10-year CVD risk should guide therapeutic considerations. It is stated in an algorithm in this guideline that moderate-intensity statin initiation is favourable for intermediate-risk adults aged 40 to 75 years old with LDL-C of 1.8 to <4.9 mmol/l (70 to <190 mg/dl) [32]. In the European Society of Cardiology (2016 ESC/EHS Guidelines for the Management of Dyslipidaemia), it is stated that immediate drug intervention is recommended along with lifestyle intervention for adults with a 10-year CVD risk of 5% or higher and LDL-C of 2.5 to <4.0 mmol/l (100 to <155 mg/dl) [33]. Similarly, the 2016 Canadian Cardiovascular Society Guidelines recommend management that includes statin therapy for individuals at intermediate-risk (10–19%, 10-year risk) with LDL-C ≥3.5 mmol/l (135 mg/dl) to decrease the risk of CVD events [34].

Our findings indicate that pharmacologic intervention can be initiated in asymptomatic pilots with intermediated-risk and LDL-C of 3.36 mmol/l (130 mg/dl). This is still consistent with the recommendations of society guidelines, and considering that our article is aimed at supporting a more aggressive approach among pilots with elevated CVD risk than in the current practices.

A study of pilot morbidity in New Zealand demonstrated that pilots had a significantly higher prevalence of medicated hypercholesterolemia than the general population (13.8% and 7.9%, respectively) [7]. Moreover, the increase in prevalence of pilots taking statins increased with age. The TC: HDL cholesterol levels, however, remain static, showing no difference between the different age groups. This finding indicates that pharmacologic intervention to hyperlipidaemia is beneficial in the pilot population.

Given the higher number of pilots who have already been treated for hyperlipidaemia without clear justifi-
cation found in the current cardiovascular guidelines, the findings from the present review provide evidence for a more appropriate threshold to be applied in initiating medication for a pilot with hypercholesterolemia. It should be noted, however, that all the available treatment options come with risks and benefits, and careful work should be done to ensure that the benefits exceed the risks. For example, medications for hypertension and diabetes mellitus can cause syncope. Particularly, risks that may compromise the safe operation of aircraft, such as adverse cognitive effects, would need to be further examined.

Patients with diabetes are considered to be CVD risk equivalent because they are at increased risk for cardiovascular events. Treating pre-diabetes to prevent the development of diabetes is therefore one of the important steps in the prevention of CVD. Pre-diabetes is a term generally used to describe a state that includes impaired glucose tolerance (IGT) or impaired fasting glucose (IFG). IGT is defined by a 2-hour postprandial glucose level of more than 140 mg/dl (7.8 mmol/l) but less than 200 mg/dl (11.1 mmol/l); and IFG is defined by a fasting plasma glucose level of 100 mg/dl (5.6 mmol/l) or greater, but less than 126 mg/dl (7.0 mmol/l) [35]. The present analysis shows that diabetes risk was highest in those who consistently had pre-diabetes despite intensive lifestyle intervention; hence treating pre-diabetes condition can significantly reduce the risk of developing diabetes. A threshold of fasting plasma glucose (FPG) ≥5.3 mmol/l (95 mg/dl) and 2-h pp ≥7.8 mmol/l (140 mg/dl) for initiating pharmacologic treatment is reasonable in a population without established CVD.

The DPP and DPPOS studies demonstrated that an intensive lifestyle intervention is effective over 10 years, and remains the best strategy for diabetes prevention. In the DPPOS trial, especially, metformin performed as well as an intensive lifestyle intervention. The overall result from the DPPOS indicated that diabetes risk was highest in those who consistently had pre-diabetes despite intensive lifestyle intervention, indicating pharmacologic intervention is reasonable in the pre-diabetes group.

The STOP-NIDDM trial also provided a similar result, despite less impressive risk reduction. Both the DPPOS and the STOP-NIDDM studies, however, provide evidence that although lifestyle changes are effective in diabetes prevention, pharmacologic intervention can also prevent conversion of impaired glucose tolerance into diabetes. Several studies have shown that the risk of a CVD event is modestly increased during the pre-diabetic condition [36]. However, there is a huge increase in risk for CVD with the development of diabetes. In addition, with the development of diabetes, permanent complications can occur that affect the eyes, kidneys, and nervous system that result in major morbidity and mortality [37].

A recent study of the successful treatment of pre-diabetes in clinical practice using physiological assessment (STOP DIABETES) supported the above findings. This was a retrospective observational study analysing 1,769 people with prediabetes, and showed that progression to type 2 diabetes in people with prediabetes can be significantly reduced with interventions designed to correct underlying pathophysiological disturbances. The study highlighted the heterogeneity of the population with prediabetes and the effectiveness of early intervention based on a personalised medicine approach [38]. In the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease, Type 2 DM is defined as a haemoglobin A1c (HbA1c) >6.5%, as an indication to start pharmacologic intervention along with lifestyle changes [32].

In relation to the cardiovascular risk estimations, the NZ CAA Civil Aviation (Examination Procedures) General Directions Notice 2009 defines some additional important risk factors [39]. This includes consideration of an applicant with impaired glucose tolerance (but not impaired fasting glucose) as diabetic. The finding of the present study supports this provision. However, the present review did not find a specific threshold for initiating treatment based on a combination of FPG and HbA1c level, as suggested by the New Zealand Primary Care Handbook 2012 [8]. None of the studies included in this review reported changes in glycosylated haemoglobin values; thus the possible clinical relevance of the findings were difficult to interpret. The American Diabetes Association (ADA) Standards of Medical Care in Diabetes-2018, however, recommended that pharmacologic intervention such as metformin can be used for younger people with pre-diabetes (HbA1c> 5.7%) [40].
The limitations of pharmacologic treatment to prevent diabetes include the risk of adverse events, the cost of medication, and the need for long-term treatment that results in a decrease in patient adherence. Moreover, some studies demonstrated that there is a high probability of glycaemic rebound after treatment cessation [35]. Because of these drawbacks, pharmacologic prevention to diabetes should not be applied as a first line strategy in the general population. This approach, however, could benefit some specific groups that have more stringent medical requirements, such as airline pilots.

Overall, the availability of interventions that have been shown to decrease the development of diabetes has indicated that pharmacologic treatment should be recommended and implemented in airline pilots with pre-diabetes, along with lifestyle changes.

Findings from the study focusing on hypertension treatment indicate that pharmacologic intervention to prehypertension condition may delay the development of hypertension. The participants in the TROPHY study were quite young, with a mean age of 48.5 years, indicating that treatment of prehypertension in younger people could also maximise the prevention of hypertension. This study, however, did not set a specific BP goal; hence the level below which BP reduction will not provide beneficial remains unknown.

A meta-analysis of randomised trials of BP reduction found that pharmacologic intervention reduced coronary heart disease events by 15% in people without a history of CVD [41]. Furthermore, this meta-analysis concluded that lowering systolic BP by 10 mmHg or diastolic BP by 5 mmHg decreases fatal and non-fatal CVD events by approximately 25%, regardless of BP level before treatment. The current NZ cardiovascular guidelines have no suggestion to treat prehypertension [8]. It is stated that within the BP range 115/70 to 170/100 mmHg, all decisions to treat should be based on the individual's cardiovascular risk. The prevalence of medicated hypertension in the pilot population and general population is not significantly different. In a New Zealand study, it was found that about 8.9% pilots were on BP lowering medication [7]. The present review provides evidence that treatment of prehypertension in the airline pilot population appears to be feasible.

Studies focusing on a multifactorial approach indicated that interventions were better than placebo in reducing cardiovascular risk. The TOGETHER and the CUSP trials, however, were considered as having high risk of bias. These trials used a small number of participants with unclear or insufficient reporting of attrition or exclusion, and the length of follow-up for these two trials were too short (6–8 weeks) leaving the implication of the studies in the CVD prevention unclear.

The ASCOT-LLA trial however, can certainly be considered in this review due to its being a large and rigorous trial comparing statin and placebo in hypertensive people. As this trial demonstrated, a significant 36% reduction in the incidence of non-fatal MI and fatal CHD was found in hypertensive people who were also treated with lipid-lowering medication, compared with those treated with anti-hypertensive only. Some limitations of this trial that could influence the results are related to the fact that the participants were primarily selected because they had high BP and were taking extensive antihypertensive medications. Hence, the absence of covariate analyses of BP data could lead to a misleading conclusion.

Overall, this finding supports the concept that treatment strategies to reduce cardiovascular disease should depend on absolute risk assessment rather than individual risk factor level. Hypertension infrequently presents alone but commonly occurs along with other cardiovascular risk factors, such as diabetes, obesity, and hyperlipidaemia. As a consequence, most guidelines incorporate the concept of global cardiovascular risk management to improve patient outcomes [42].

Limitations of this review

The drawbacks of the present review include the use of trials that had short follow-up times, while meaningful predictions of cardiovascular event risk usually encompass a 10-year period. Most of the included trials were stopped early because of a highly statistically significant reduction in cardiovascular events for patients randomised to intervention (drug) groups. Another consequence is that less data are available on the long term safety of reducing the individual risk factors to low levels with the medications used.

The trials also generally included participants selected on the basis of stringent eligibility criteria. The
participants were generally healthier and had better compliance to treatment compared with patients in clinical practice. We should be cautious about generalising the results to a wider population. Special considerations should be taken into account when applying the results of this study to aviators. Early interventions may result in flying restrictions due to side effects of the medications.

Most of the trials also pointed out that the cost-effectiveness of the interventions remains uncertain for the general population and were concerned about the costs of the medications used. This might not be a problem in airline pilots who are required to have a high level of fitness, but who enjoy a high socioeconomic status [7].

Another drawback of the present review is related to drawing conclusions from studies which use surrogate markers of risk as outcome measures. This is relevant to the treatment of ‘pre-hypertension’ to reduce the risk of ‘hypertension’ (TROPHY, TOGETHER and CUSP studies), and the use of ‘diabetes’ (DPP, DPPOS and STOP-NIDDM studies) as the outcome in clinical trials. Use of surrogates is frequently hampered by the fact that the evaluation of their association with relevant clinical endpoints may be lacking, insufficient or inaccurate.

Despite all of the limitations, the present review provides information on the benefits of lowering the risk factors applied to people in categories in which the NZ Cardiovascular Guidelines can not make definitive recommendations about drug therapy.

**Conclusion**

The present review demonstrates that pharmacologic interventions are preferred, and in asymptomatic people should be interpreted in the context of their absolute cardiovascular risk. In an occupational group such as the airline pilot population, the implementation of these findings appears to be feasible. In combination with the current CVD management guidelines, a more aggressive approach to cardiovascular risk in pilots means that, among pilots with a 5-year CVD risk of 5–10% and 10–15%, the presence of individual risk factors such as prehypertension, pre-diabetes or a LDL-C of ≥ 3.36 mmol/l (130 mg/dl) should be managed with drug intervention in addition to lifestyle changes. This review demonstrates that the available evidence from large quality trials supports a more aggressive approach to managing hyperglycaemia, hyperlipidaemia, and hypertension in asymptomatic people with a low-intermediate CVD risk.

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無症候性成人の心血管疾患リスク要因の修正とパイロットへの影響

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要 旨: この研究は、低から中程度の心血管疾患リスクを持つ無症候性の人々を管理する際により積極的なアプローチを支える利用可能な証拠を調べ、高血糖、高脂血症、高血圧の服薬治療を開始するための適切な閾値を評価し、航空会社のパイロットへの影響を示すことを目的とする。すべてのEBMレビュー、EMBASE、およびOvid MEDLINEデータベースを含むOvidSPインターフェイスを使用して、体系的な検索を実施した。データーには16件のランダム化比較試験が含まれ、服薬治療を開始するための適切な閾値が抽出された。高脂血症の治療に関する研究では、中リスクの人々の介入開始の閾値は3.36 mmol/l(130 mg/dl)のLDL-Cレベルであることが示された。下限またはさらなる減少が有益とならない最適なLDL-Cレベルはなかった。高血糖症の治療に関する研究では、空腹時血糖グルコースの閾値が5.3 mmol/l以上(95 mg/dl)であり、2時間の食後グルコースレベルが7.8 mmol/l(140 mg/dl)であることが服薬治療の開始に妥当であることが示唆された。血圧が≥130/≤89 mmHgまたは≤139/≥85 mmHgの人に治療を開始すると、ステージ1高血圧発症リスクが大幅に減少した。多因子介入研究では、高血圧患者(BP≥160/≥100 mmHg)で、総コレステロール6.5 mmol/l(251.35 mg/dl)以上の患者への治療を開始すると、致死性および非致死性心血管イベントの発生の大幅なリスク削減をもたらした。大规模な試験から得られた証拠は、5年のCVDリスクが5-10%および10-15%の無症候性パイロットの高血糖症、高脂血症、高血圧の管理におけるより積極的なアプローチを支えている。

キーワード：心血管リスク、航空会社パイロット、無症候性人口、リスク低減。

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