UNIVERSITY OF BIRMINGHAM

Literature Search on

Left Ventricular Ejection Fraction

Aggressive Research Intelligence Facility
West Midlands Health Technology Assessment Collaboration

February 2007

For the Drivers Medical Group
DVLA
Swansea

ARIF

WMHTAC
West Midlands HTA Collaboration

About ARIF and the West Midlands Health Technology Assessment Collaboration

The West Midlands Health Technology Assessment Collaboration (WMHTAC) is an organisation involving several universities and academic groups who collaboratively produce health technology assessments and systematic reviews. The majority of staff are based in the Department of Public Health and Epidemiology at the University of Birmingham. Other collaborators are drawn from a wide field of expertise including economists and mathematical modellers from the Health Economics Facility at the University of Birmingham, pharmacists and methodologists from the Department of Medicines Management at Keele University and clinicians from hospitals and general practices across the West Midlands and wider.

WMHTAC produces systematic reviews, technology assessment reports and economic evaluations for the UK National Health Service's Health Technology Assessment (HTA) programme, the National Institute for Health and Clinical Excellence (NICE). Regional customers include Strategic Health Authorities, Primary Care Trusts and regional specialist units. WMHTAC also undertakes methodological research on evidence synthesis and provides training in systematic reviewing and health technology assessment.

The two core teams within WMHTAC are the Aggressive Research Intelligence Facility (ARIF) and the Birmingham Technology Assessment Group (BTAG)

ARIF provides a rapid on-demand evidence identification and appraisal service primarily to commissioners of health care. Its mission is to advance the use of evidence on the effects of health care and so improve public health. The rapid response is achieved by primarily relying on existing systematic reviews of research, such as those produced by the Cochrane Collaboration, the National Institute for Health and Clinical Excellence (NICE), the NHS Centre for Reviews and Dissemination, and the NHS Health Technology Assessment (HTA) programme. In some instances, longer answers to questions are required in which case mini rapid reviews of existing systematic reviews and key primary studies are compiled, typically taking 1-2 months to complete.

Occasionally a full systematic review is required and then topics are referred to BTAG who coordinate the production of systematic reviews for several customers under a number of contracts. ARIF is intrinsically involved in the production of these systematic reviews.

Aggressive Research Intelligence Facility (ARIF)
West Midlands Health Technology Assessment Collaboration (WMHTAC)
Department of Public Health and Epidemiology
University of Birmingham
Birmingham
B15 2TT

arifservice@bham.ac.uk
0121 414 3166

1 Aims

The aims of this report were to address the following questions submitted by the Drivers Medical Group.

1.1 Primary Question

What proportion of those who complete three stages of the standard Bruce electrocardiogram (ECG) exercise test (Bruce protocol)[A] have a left ventricular ejection fraction (LVEF) of less than 40%?

1.2 Secondary Question

What additional factors identify those who have undergone coronary artery bypass grafting (CABG), but are at an increased risk of a further sudden cardiac event post-procedure assuming that their LVEF post procedure (3 months at least) is 40% or more?

Further details are given in the request submitted by the Drivers Medical Group (Appendix 1 – Details of Request).

2 Background

There are about 1.7 million driving licence holders who have Group 2 entitlement. Their licences expire initially at the age of 45 years, and are then renewable every five years until the age of 65, and annually thereafter. For an applicant or driver who has been permitted to hold a Group 2 driving licence after cardiac assessment, a short-term licence (maximum duration 3 years) will usually be issued and will be renewable on receipt of satisfactory medical reports.[1]

A medical examination is required on first issue and for re-licensing to evaluate fitness to drive. The definition of fitness to drive for Group 2 is a risk of a disabling event of 2% or less per annum, which is assumed to equate to a cardiovascular event rate of 2% or less per annum, and in turn to equate to a total mortality of 1% or less per annum. [1]

Impaired LVEF is associated with sudden cardiac events causing incapacity. The critical tipping point is 40%. Below this level incapacitating events increase exponentially. A documented LVEF of <40% debars Group 2 licensing (Appendix 1 – Details of Request).

The current practice in issuing licences for Group 2 drivers is based upon an algorithm of investigation of ischemic heart disease. Firstly, the standard Bruce electrocardiogram test is performed on a treadmill or bicycle. Drivers should be able to complete 3 stages of the Bruce protocol or 10.5 metabolic equivalents[B]

[A] The standard Bruce electrocardiogram exercise test is a standard procedure with a range of cardiovascular purposes, such as the diagnosis of angina, risk stratification of mycordial infarction, evaluation of exercise tolerance and cardiac function. The individual uses an exercise treadmill while connected to an electrocardiogram machine and, in the Standard Bruce Protocol, undergoes up to seven three-minute exercise stages. The Driver and Vehicle Licensing Agency test for Group 2 drivers considered at risk of a cardiovascular event requires completion of stage III of the Bruce Protocol, which equates to an exercise level of 10.5 metabolic equivalents off cardioactive medication.

[B] Metabolic equivalent is a measure of the level of exercise. One MET is equivalent to the energy expended at rest, or 3.5 ml O2 per kg body mass per minute.

(MET) safely, without anti-angina medication for 48 hours and should remain free from signs of cardiovascular dysfunction. Secondly, for those who cannot complete 9 minutes exercise due to a non-debarring condition and have equivocal ECG change and no cardiac symptoms, myocardial perfusion scintigraphy[C] or stress echocardiography[D] should then be carried out. The standard requires that no more than 10% of the myocardium is affected by reversible ischemic change and in addition the LVEF must be demonstrated to be 40% or more.[1]

Although it is unlikely that many people could achieve the exercise test requirements with a LVEF of <40%, there is concern and anecdotal case evidence that some have managed the exercise test requirement despite impaired LVEF (<40%), who therefore remain at high risk of a cardiac event.

Another concern is whether we can identify a group of significantly higher risk CABG cases who therefore need closer scrutiny than the usual 3 year licensing period.

3 Methods

To address the questions raised by the Drivers Medical Group, outline methods are listed as follows.

- To undertake searches for diagnostic test accuracy studies which assess the results of the standard Bruce electrocardiogram test relative to LVEF as measured by echocardiography and myocardial perfusion scintigraphy for individuals with suspected or confirmed ischaemic heart disease. Further, to search for prognostic studies of CABG patients.
- To select studies based on the following inclusion criteria: For the primary question, studies conducted Bruce electrocardiogram test with exercise capacity data available and/or conducted echocardiography or myocardial perfusion scintigraphy with LVEF values available. For the secondary question, studies with long term (> 1 year) follow-up of CABG patients with LVEF of more than 40%.
- Studies that required translation were excluded due to the time frame available for this report.
- To comment upon methodologiclal quality of the selected studies using criteria for assessment of observational studies, particularly cohort studies.[2]
- To extract and tabulate the relevant outcomes where appropriate and possible.
- To analyse information identified where appropriate and possible.

[C] Myocardial perfusion scintigraphy uses radioactive tracers to image a combination of myocardial perfusion and viability. It requires the intravenous injection of small amounts of the tracer at rest and during exercise. The tracer accumulates into viable myocardium in proportion to perfusion and its distribution within the myocardium is detected using a gamma camera.

[D] Stress echocardiography uses ultrasound to record images of the heart before and after exercise. Exercise can be mimicked by injecting dobutamine to increase the heart rate and workload. The technique is used to monitor for reduced blood flow to the heart, and, therefore, whether the heart is receiving sufficient oxygen during exercise.

3.1 Searches

3.1.1 Existing reviews

Searches to identify existing systematic reviews or primary studies on this topic were performed by an information specialist utilising the ARIF search protocol (Appendix 2 – Search strategies).

3.1.2 Primary studies

3.1.2.1 Proportion of those who complete three stages of the standard Bruce electrocardiogram exercise test with a LVEF of less than 40%

Searches were undertaken for diagnostic test accuracy studies in MEDLINE (Ovid) 1950 – Jan 2007, EMBASE (Ovid) 1980 – Week 4 2007, and the Cochrane Library (2007 Issue 1, Wiley Internet version). The search strategy combined MeSH headings where appropriate and text terms for Bruce protocol, exercise stress testing or exercise tolerance with MeSH and text terms for echocardiography or cardiac output, stress echocardiography or myocardial perfusion scintigraphy with MeSH and text terms for LVEF or cardiac output. Methods 'filters' for diagnosis were also used. The strategy was developed iteratively and modified accordingly.

The detailed search strategies can be found in Appendix 8.2.2 – Search strategies.

A research analyst and an information specialist formulated the search strategy. Searches were undertaken by an information specialist.

3.1.2.2 Risk factors associated with sudden cardiac event of CABG patients

Searches were undertaken in MEDLINE (Ovid) 1950 – Jan 2007, EMBASE (Ovid) 1980 – Week 5 2007 and the Cochrane Library (2007 Issue 1, Wiley Internet version). The search strategy employed MeSH headings where appropriate and text terms for CABG or coronary artery bypass with MeSH headings and text terms for LVEF or cardiac output. A prognosis methods 'filter' was also used.

A research reviewer scanned the search results for relevance based on information in the title and abstract. Articles that contained some patients with LVEF of more than 40% who had undergone CABG were obtained in full for further scrutiny.

4 Results

The searches retrieved a total of 548 articles. The titles and abstracts were scanned and 59 articles (30 articles addressing the primary question and 29 articles addressing the secondary question) were selected and requested in full.

4.1 Results for the proportion of those who complete three stages of the standard Bruce electrocardiogram exercise test with a LVEF of less than 40%

None of the thirty potentially relevant studies contained information which directly addressed the. Twenty-nine of these studies did not contain both exercise capacity and LVEF values. Although the study by

Mathenthiran[3] contained exercise capacity and LVEF values, it cannot be used to directly address the question. This is because only means and standard deviations of LVEF and exercise capacity values were reported, making it impossible to directly estimate the proportion of those who completed three stages of the standard Bruce electrocardiogram exercise test with a LVEF of 40% or less.

On this basis it seems that the relation between completing three stages of 9 minutes exercise duration and a LVEF of more than 40% was probably not established directly through diagnostic studies. We therefore decided to address the question using an indirect method. The proportion of those who achieved a certain exercise capacity in a Bruce electrocardiogram exercise test, e.g. y MET, with a LVEF of 40% or less can be estimated using Equation 1.

Equation 1: $P_{EC>y} = P_{LVEF>0.4}(1-x) + P_{LVEF\leq 0.4}x$

Where, $P_{EC>y}$ is the mortality rate for those who had an exercise capacity of more than y MET, $P_{LVEF>0.4}$ is the mortality rate for those who had a LVEF of more than 40%, and $P_{LVEF\leq 0.4}$ is the mortality rate for those who had a LVEF of 40% or less. *x* is the proportion of those who achieved an exercise capacity of more than *y* MET with a LVEF of 40% or less.

The Equation 1 is just an expression of the fact that the overall mortality/cardiac event rate for those who have an exercise capacity of more than y MET is the sum of mortality/event rates in those with LVEF above and below 40%, multiplied in each case by proportion in each category. If we know the mortality/event rates for all categories we can use simple algebra to calculate possible values of x, the proportion in whom LVEF ≤40%.

Eleven studies[3-13] that contained mortality/cardiac event rates for those who experienced Bruce exercise-tolerance electrocardiogram testing or experienced either stress echocardiography or myocardial perfusion scintigraphy with LVEF available were selected to address the question. Nineteen studies were excluded because they did not contain relevant information about exercise capacity or LVEF.

The eleven selected studies were cohort studies where patients underwent exercise-tolerance electrocardiogram testing with exercise capacity available or underwent stress echocardiography or myocardial perfusion scintigraphy with LVEF available. They were prospectively followed up for at least one year. The follow-up was obtained by physician-directed telephone interview using a standardised questionnaire or by the social security death index. Some studies did not report follow-up rate at all. A few studies reported a follow-up rate of more than 90%, but did not give reasons for loss to follow-up. Most studies took all-cause mortality as the end point of interest, only a few reported cardiac related event rates where cardiac death was confirmed by review of hospital medical records and/or death certificate and myocardial infarction was confirmed by evidence of a combination of clinical symptoms and ECG and cardiac enzyme changes.

Four studies reported results of exercise testing and the long-term mortality/event rates (Table 1, page 7). A similar protocol was used in these studies. The study by Mathenthiran[3] used exercise treadmill testing according to the standard Bruce's protocol. The studies by Myers[4] and Vivekananthan[6] used symptom-

limited treadmill testing according to standardized graded or individualised ramp-treadmill protocols. The study by Shaw[5] used Bruce or modified Bruce protocol. Event-free survival curves were reported in all these studies. The event rates at different time points were abstracted from the tables or text or measured manually from the survival curves reported in these studies. Some studies reported overall mortality rate, while others reported cardiac death rates or cardiac event rates which were defined as cardiac death or myocardial infarction. The exercise capacities and their corresponding event rates are plotted in Figure 1, page 8. The scatter plot shows that in general the mortality/event rate increases as exercise capacity decreases.

Table 1 Relationship between exercise capacity and mortality/event rates

Study	Population (N)	Age years mean±SD	Male (%)	Workload mean±SD	Event rate 1 year (%)	Event rate 2 year (%)	Event rate 3 year (%)	Event rate 5 year (%)
Mahenthiran[3]2005	Subjects (1268)	60±12	52	8.7 ± 3.3 (MET)	1[a]	2.1[a]	4.3[a]	
				6.5 ± 4.1 (MET)	1.5[a]	3.1[a]	6.3[a]	
Myers[4] 2002	Subjects[b] (2534)	55±12	100	>8 (MET)	1.0[c]		1.5[c]	2.5[c]
				5-8 (MET)	2[c]		5[c]	10[c]
				<5 (MET)	4[c]		14[c]	25[c]
	Subjects[d] (3679)	61±10	100	>8 (MET)	1.4[c]		4[c]	7.5[c]
				5-8 (MET)	3[c]		6[c]	17.5[c]
				<5 (MET)	5[c]		15[c]	27.5[c]
Shaw[5] 2003	Subjects[e] (3168)	61±13	52	8.6 ± 7 (minutes)	0.6[f]	1.4[f]		
Vivekananthan[6] 2003	Subjects[g] (2935)	59±10		7.5 (MET)	1.1[c]	2[c]	2.5[c]	5[c]

a: cardiac event rate (death or myocardial infarction)
b: those who had no evidence of cardiovascular disease
c: overall mortality rate
d: those who had evidence of cardiovascular disease with an abnormal exercise test result (ST-segment depression of ≥ 1.0mm, exercise induced angina, or both) or a history of cardiovascular disease
e: those who had normal or low risk of coronary disease (summed stress score <4)
f: cardiac mortality rate
g: those who underwent symptom-limited exercise testing for suspected coronary artery disease

The study by Shaw[5] reported the event rates for those who had an average of 8.6 minutes exercise time with a standard deviation of 7 minutes. The results from this large multi-centre registry showed that the annual cardiac death rate was 0.6% for individuals with normal or low risk of coronary heart disease.

The study by Myers[4] reported the overall mortality rates for subjects who had a history of cardiovascular disease or an abnormal exercise result, or both, and for normal subjects who had no evidence of cardiovascular disease. After adjustment for age, the peak exercise capacity measured in MET was a strong

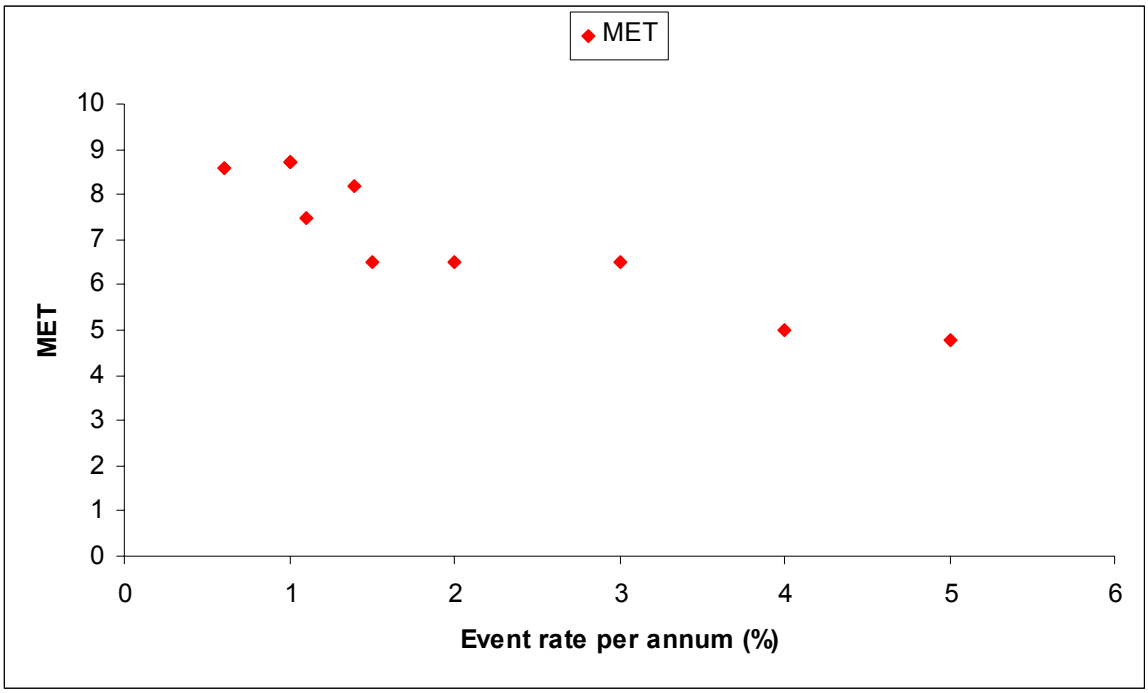

Figure 1 Mortality/event rate per annum varies as exercise capacity changes

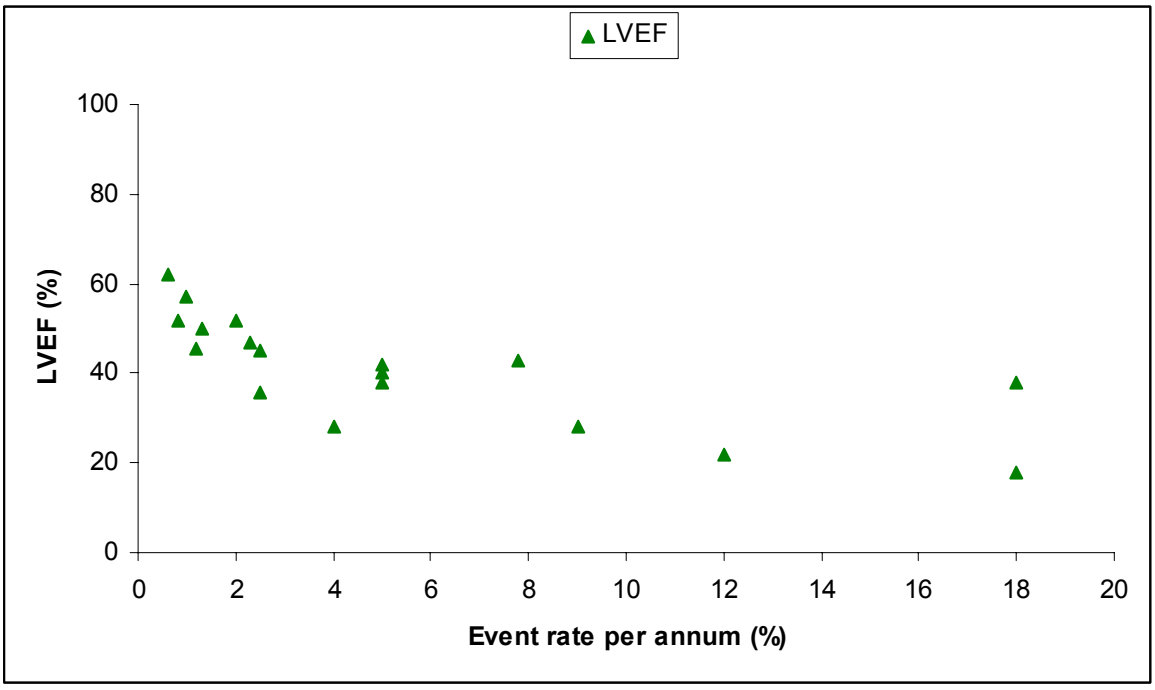

Figure 2 Mortality/event rate per annum varies as LVEF changes

predictor of risk of death among both normal subjects and those with cardiovascular disease. The mortality rates where exercise capacity was more than 8 METs were 1% for normal subjects and 1.4% for those with cardiovascular disease. These death rates were all cause. The specific causes of death were not reported.

The exercise-capacity data were estimated in this study on the basis of the speed and grade of the treadmill, rather than directly measured exercise capacity which is known to be a more accurate and reproducible measure of exercise tolerance. The findings were applicable only to men.

Table 2 Relationship between LVEF and event rates

Study	Population (N)	Age years mean±SD	Male (%)	LVEF (%) mean±SD	Event rate 1 year (%)	Event rate 2 year (%)	Event rate 3 year (%)	Event rate 5 year (%)
Mahenthiran[3]2005	Patients (1268)	60±12	52	57 ± 8	1.0[a]	1.1[a]	3[a]	
				45 ± 12	2.5[a]	5[a]	10[a]	
Watanabe[7] 2001	Patients[b] (5438)	58±11	63	>50	0.8[c]	1.5[c]	2[c]	
				41-50	1.2[c]	2.5[c]	4[c]	
				31-40	2.5[c]	5[c]	6[c]	
				<30	4[c]	13[c]	16[c]	
D'Andrea[8] 2003	Diabetic patients (325)	59±9	61	>40	5[d]	7[d]	10[d]	
				<40	18[d]	28[d]	32[d]	
Nishiyama[9] 1995	Patients[e] (220)	56±7	92	≥60	0.6[d]	1[d]	1[d]	3[d]
				41-59	1.3[d]	5[d]	7[d]	7[d]
				≤40	5[d]	13[d]	18[d]	23.8[d]
Supino[10] 1994	CABG patients (41)	70±4		≥45	2.3[c]			
				<45	7.8[c]			
Talwalkar[11] 1996	CABG patients (100)	82±3	64	>20	12[c]	17[c]	19[c]	
				≤20	18[c]	36[c]	68[c]	
Appoo[12] 2004	CABG patients (7841)	65	80	>50	2[c]	3.5[c]	5[c]	8.8[c]
				30-50	5[c]	7[c]	9[c]	14.5[c]
				<30	9[c]	12.5[c]	15[c]	22.3[c]
Formica[13] 2006	CABG patients (271)	56±7	95	55±7	2.6[d]		3[d]	3.4[d]

a: cardiac event rate (death or myocardial infarction)

b: those without a history of heart failure or valvular disease

c: overall mortality rate

d: cardiac mortality rate

e: those with double or triple vessel disease whose coronary arteriograms showed significant stenosis of their major coronary arteries.

Eight studies reported results of long-term cardiac and mortality event rates with different LVEF values (Table 2, page 9). These eight studies had different populations, the average age varying from 56 to 82, and proportion of male patients varying from 52% to 95%. Most studies reported overall mortality rates. Only a few reported cardiac death rates, the study by Mahenthiran[3] reported cardiac event rates. The values of

LVEF and the corresponding mortality/event rates are plotted in Figure 2, page 8. The scatter plot shows that in general the mortality/event rate increases as LVEF decreases.

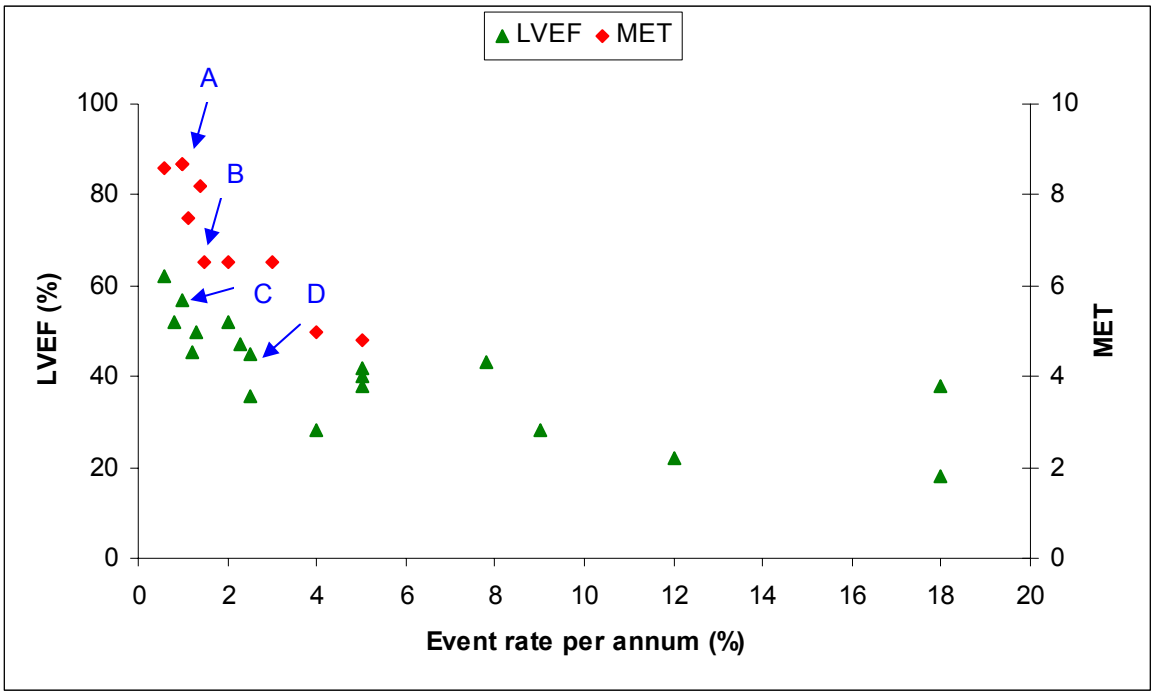

Figure 3 Mortality/event rate per annum varies as exercise capacity or LVEF changes

Figure 3 shows the scatter plots of mortality/event rates and both exercise capacity and LVEF. Only one study by Mahenthiran[3] reported both exercise capacity and LVEF in relation to these mortality/event rates. Points A and B in Figure 3 showed that the cardiac event rates were 1% for patients who achieved an exercise capacity of 8.7± 3.3 METs and 1.5% for patients who achieved an exercise capacity of 6.5 ± 4.1 METs. Points C and D in Figure 3 showed that the cardiac event rates were 1% for patients who had a LVEF of 57 ± 8% and 2.5% for patients who had a LVEF of 45 ± 12%. However, because the exercise capacity and LVEF were reported in a format of mean ± standard deviation it is impossible to abstract the cardiac event rate for a certain value of exercise capacity and a certain value of LVEF. Figure 3 also showed that the mortality/event rates for those who had a LVEF of more than 40% varied from 0.6% to 5% and that the mortality/event rates for those who had a LVEF of 40% or less varied from 4% to 18%. These are probably because the populations in these studies were different.

In order to estimate the proportion of those who completed an exercise capacity of more than 8 METs with a LVEF of 40% or less using Equation 1, we calculated the overall mortality rate for those who had a LVEF of more than 40%, the mortality rate for those who had a LVEF of 40% or less, and the mortality rate for those who achieved an exercise capacity of more than 8 METs. We only used the studies in which above or below 40% of LVEF was clearly defined. The studies that reported LVEF as mean ± standard deviation were excluded from this analysis.

Because the mortality/event rates varied a lot between different types of populations, the analyses were performed separately for patients who had history of heart disease or were suspected of having heart disease, diabetic patients and patients with CABG. The estimated mortality rates are listed in Table 3. The calculations are showed in the notes of Table 3.

Table 3 Proportions of those who complete exercise capacity of more than 8 METs in the standard Bruce electrocardiogram exercise test with a LVEF of 40% or less

Patient category	Mortality rate MET>8	Mortality rate LVEF>40%	Mortality rate LVEF≤40%	% of LVEF>40% given MET>8	% of LVEF≤40% given MET>8
Patients with history of heart disease or suspected of having heart disease	1.2[a]	0.98[b]	3.83[c]	92.3	7.7
Diabetic patients	1.2[a]	5[d]	18[e]	100	0
Patients with CABG	1.2[a]	2.15[f]	13.5[g]	100	0

a: averaging of mortality rates of those who achieved an exercise capacity of more than 8 METs from the study by Myers[4], (1.0+1.4)/2

b: averaging of mortality rates of those who had a LVEF of more than 40% from the studies by Watanabe[7] and Nishiyama[9], (0.8+1.2+0.6+1.3)/4

c: averaging of mortality rates of those who had a LVEF of 40% or less from the studies by Watanabe[7] and Nishiyama[9], (2.5+4+5)/3

d: mortality rate of the diabetic patients who had a LVEF of more than 40% from the study by D'Andrea[8]

e: mortality rate of the diabetic patients who had a LVEF of 40% or less from the study by D'Andrea[8]

f: averaging of mortality rates of CABG patients who had a LVEF of more than 40% from the studies by Supino[10] and Appoo[12], (2.3+2)/2

g: averaging of mortality rates of CABG patients who had a LVEF of 40% or less from the studies by Talwalkar[11] and Appoo[12], (18+9)/2

For patients who had history of heart disease or were suspected of having heart disease, the mortality rates were 1.2% for those who achieved an exercise capacity of more than 8 METs, 0.98% for those who had a LVEF of more than 40% and 3.83% for those who had a LVEF of 40% or less. The upper limit of proportion of those who had a LVEF of 40% or less, given that their exercise capacity was more than 8 METs, is estimated to be 7.7%. With a MET value of 10.5 (the true equivalent of completing Bruce stage III), the estimate would be less.

For diabetic patients, the mortality rates were 5% for those who had a LVEF of more than 40% and 18% for those who had a LVEF of 40% or less. The proportion of diabetic patients who achieved an exercise capacity of more than 8 METs with a LVEF of 40% or less is close to 0%.

For CABG patients, the mortality rates were 2.15% for those who had a LVEF of more than 40% and 13.5% for those who had a LVEF of 40% or less. The proportion of CABG patients who achieved an exercise capacity of more than 8 METs with a LVEF of 40% or less is close to 0%.

4.2 Results for risk factors associated with sudden cardiac event of CABG patients

Twenty-nine potential studies were identified. Five[14-18] of them contained relevant information to identify additional risk factors of a further sudden cardiac event for those who had undergone CABG with their LVEF post procedure (3 months at least) of more than 40%. The other twenty-four studies were excluded because CABG patients did not have a LVEF of more than 40%.

These five studies and the three studies[10 11 13] which were also used to address the primary question, were used to address this question. All the eight studies were cohort studies. Clinical follow-up was obtained by periodic telephone interview or mailed questionnaire to each patient, family members, or patient's physician for most studies. The study by Mistiaen[17] tracked patients lost to follow-up and reported the dates and causes of death. Some studies reported pre-operation LVEF values, others did not mention the time at which LVEF values were measured.

The prognostic indices of sudden event rates, including cardiac mortality rate, myocardial infarction, or overall mortality rate, are summarised in Table 4, page15. Three studies by Supino,[10] Mistiaen,[17] and Formica[13] showed that age is a risk factor of a sudden event. In the study by Supino,[10] the rates of death, myocardial infarction, or cardiac surgical procedures were 10.4% for the higher age group (greater than 70 years) and 5.7% for the lower age group (less than or equal to 70 years). However, this was not statistically different with a p-value of 0.065.The study by Mistiaen[17] gave overall mortality rates of 2.5% for the higher age group (greater than or equal to 73 years) and 2.0% for the lower age group (less than 73 years), which was significantly different with a p-value of 0.0067. The study by Formica[13] also showed that age was a significant predictor of late cardiac death, with a p-value of 0.004 and hazard ratio (HR) of 1.12.

The two studies by Talwalkar[11] and Myler[18] investigated whether gender is a risk factor for sudden events. The study by Talwalkar[11] gave overall death rates of 5.5% and 3.6% for male and female patients, respectively, showing that men had a 2% greater risk of death after undergoing CABG surgery, but that such a difference was not significantly different with a p-value of 0.577. The study by Myler[18] performed multivariate analysis and the results showed that being female was a significant predictor of late death compared to male. The age and LVEF values of patients between the two studies were different. The study by Myler[18] contained young patients (62 years ± 9) with 67% of patients having LVEF of greater than 45%, while the study by Talwalkar[11] contained older patients (82 years ± 3) with a LVEF of 42±12%.

The four studies by Luciani,[14] Hakala,[15] Ono,[16] and Mistiaen[17] investigated prognosis of cardiac events for diabetic patients. CABG patients with insulin dependent diabetes had an overall death rate of 9.7%, which

was significantly different (p<0.001) compared to 3.3% for the patients with non-insulin dependent diabetes. The cardiac mortality rates for CABG patients with or without diabetic retinopathy were 3.5% and 0.6% respectively, which was significantly different with a p-value less than 0.001. The cardiac or overall mortality rates for patients who underwent CABG with diabetes varied from 2.5% to 3.1% compared to 1.2% to 2.3% for the patients who underwent CABG without diabetes. The differences of the mortality rates between patients with or without diabetes were significant with p-values less than 0.05. The study by Mistiaen[17] reported that the median survival times were 33 (15-67) months for CABG patients with diabetes and 48 (24-70) months for CABG patients without diabetes.

It is important to note that many cardiac event rates for post CABG (mean LVEF >40%) exceed 1% irrespective of other risk factors, suggesting that CABG alone may be associated with a level of risk similar to those who have not had CABG but who have a LVEF of 40% or less. However, the cardiac event rates were calculated from post CABG patients who had a mean of LVEF over 40%. A proportion of the post CABG patients may have a LVEF below 40%. The study by Supino[10] reported that the overall mortality rate was 2.3% for post CABG patients with a LVEF above 45%. But it is a small study with 41 patients. Other risk factors which increase risk further in post CABG (mean LVEF >40%) included endocarditis, carcinoma, previous CABG surgery, dyslipidemia, preoperative intraaortic balloon pump, previous aortic valve replacement and perioperative myocardial infarction. All the factors, except for previous CABG surgery and previous aortic valve replacement, were significantly associated with cardiac events.

5 Conclusion

We found four studies that reported mortality/cardiac event rates for those patients who had different exercise capacity values and eight studies that reported mortality/cardiac event rates for those patients who had various LVEF values. For patients who had a history of heart disease or were suspected of having heart disease, the mortality rates were 1.2% for those who achieved an exercise capacity of more than 8 METs, 0.98% for those who had a LVEF of more than 40% and 3.83% for those who had a LVEF of 40% or less. The upper limit of proportion of those who had a LVEF of 40% or less, given that their exercise capacity was more than 8 METs, has been estimated to be 7.7%. With a MET value of 10.5, the estimate would be less. For diabetic patients, the mortality rates were 5% for those who had a LVEF of more than 40% and 18% for those who had a LVEF of 40% or less. The analysis results suggested that none of the diabetic patients who achieved an exercise capacity of more than 8 METs would have a LVEF of 40% or less. For CABG patients, the mortality rates were 2.15% for those who had a LVEF of more than 40% and 13.5% for those who had a LVEF of 40% or less. The analysis results suggested that none of the CABG patients who achieved an exercise capacity of more than 8 METs would have a LVEF of 40% or less.

We identified eight studies to investigate additional risk factors for patients who underwent CABG with a mean LVEF of more than 40%. The results suggested that apart from LVEF, the significant risk factors of sudden cardiac events include diabetics, age, endocarditis, carcinoma, dyslipidemia, preoperative intraaortic balloon pump, and perioperative myocardial infarction. One study reported that the median survival times were 33 (15-67) months (less than 3 years) for patients with diabetes and 48 (24-70) months for patients without diabetes.

Finally, in the course of this request, we have not become aware of any evidence about how the 1% of mortality threshold (which is corresponding to 2% of cardiovascular event rate) was established, or indeed how cumulative mortality/event rates over a number of years are dealt with. This suggests an interesting area for enquiry, alongside the probable need for primary research in more direct measurement of the relationship between exercise stress test findings and LVEF.

6 Limitations of this report

This is not a systematic review but a rapid assessment of relevant literature. Although the search strategies were broad and comprehensive for both systematic reviews and primary studies, and the equivalent of many reviews which claim to be systematic, some relevant studies may have been missed. This is particularly so given that observational study designs were being targeted.

Some event rates at different time points were measured manually from the survival curves using a ruler. This might affect the estimate accuracy of the event rates, however, it would not be expected to impact on the estimate of the upper limit of the proportion of those who have an exercise capacity of more than 8 METs, and a LVEF of 40% or less. This is because the event rates for both those who had an exercise capacity of more than 8 METs and those who had a LVEF of above or below 40% were measured in the same way.

To investigate additional risk factors of sudden cardiac event for those patients who underwent CABG with LVEF of more than 40%, studies with a mean LVEF of more than 40% (approximate standard deviation of 10) were selected. Some patients might have a LVEF of less than 40%. However, because the studies did not contain individual patient data it is impossible to look at only those patients whose LVEF was more than 40%. Another limitation is that LVEF values might not always be measured after CABG surgery. Some studies reported pre-operation LVEF values, while others did not mention when LVEF values were measured.

Finally it should be re-emphasised that the proportion of those who have LVEF of 40% or less given that they complete 3 stages of exercise ECG testing has been estimated using an indirect method. This is highly susceptible to bias and confounding. If the question is important, a direct measure of the relationship between exercise stress testing and LVEF should be obtained. Further, if this direct measurement reveals no close relationship between exercise testing results and LVEF, then the inevitable conclusion must be that LVEF itself must be directly measured on all group 2 driving applicants too.

Table 4 Prognostic indexes of mortality/event rates for patients who underwent CABG surgery

Study	Population (N)	Age years mean±SD	Male (%)	LVEF (%)	Risk factor	Mean survival time, in months (range)	Event rate 1 year (%)	Event rate 2 year (%)	Event rate 3 year (%)	Event rate 5 year (%)	P-value
Supino[10] 1994	CABG patients (41)	70±4	93	47.9±12	Age >70		10.4[a]			29.5[a]	P=0.065
					Age ≤70		5.7[a]			10.5[a]	
					LVEF ≥ 45		2.3[b]			0[b]	P=0.038
					LVEF < 45		7.8[b]			23.5[b]	
Talwalkar[11] 1996	CABG patients (100)	82±3	64	42±12	Male		5.5[c]				P=0.577[d]
					Female		3.6[c]				
Luciani[14] 2003	CABG patients with type II diabetes (200)	66±8	68	45±12[e]	Insulin dependent		9.7[c]				P<0.001
		63±10	58	43±10[e]	Non insulin dependent		3.3[c]				
Hakala[15] 2005	CABG patients (1732)	63±8	75	62±14[e]	Diabetics		2.5[f]			4[f]	P=0.02
				63±14[e]	Non-diabetics		1.2[f]			3[f]	
				62±14[e]	Diabetics		4[b]			11[b]	P=0.001
				63±14[e]	Non-diabetics		1.5[b]			6[b]	
Ono[16] 2002	CABG patients with type II diabetes (223)	61±8	76	52±11[e]	Diabetics with retinopathy		3.5[f]				P<0.001
		60±9	68	54±13[e]	Diabetics without retinopathy		0.6[f]				
Mistiaen[17] 2001	CEPB patients, 70% CABG (400)	Median 73 Range (46,92)	56	Median 66 (70% above the median)	LVEF ≥ 66	51 (35-77)	1.3[c]				P=0.0001
					LVEF < 66	33 (20-43)	3.4[c]				
					Endocarditis	28 (2-53)	4.1[c]				P=0.0029
					No endocarditis	51 (26-70)	2.3[c]				

Study	Population (N)	Age years mean±SD	Male (%)	LVEF (%)	Risk factor	Mean survival time, in months (range)	Event rate 1 year (%)	Event rate 2 year (%)	Event rate 3 year (%)	Event rate 5 year (%)	P-value
					Carcinoma	22 (15-52)	3.3 [c]				P=0.005
					No carcinoma	50 (25-73)	2.2 [c]				
					Age (≥73)	39 (18-68)	2.5 [c]				P=0.0067
					Age (<73)	55 (33-87)	2.0 [c]				
					Diabetes	33 (15-67)	3.1 [c]				P=0.048
					No diabetes	48 (24-70)	2.3 [c]				
					Previous CABG	35 (21-49)	1.8 [c]				NS
					No previous CABG	52 (27-71)	2.0 [c]				
					Previous AVR	49 (40-71)	4.5 [c]				NS
					No previous AVR	50 (33-71)	2.3 [c]				
Myler[18] 1994	CABG patients (85)	62±9		>45 (67%)	Female						P<0.001[h]
					Male						
Formica[13] 2006	CABG patients (271)	56±7	95	55±7 [e]	Age		HR=1.12[i]				P=0.004
					Dyslipidemia		HR=6.5[i]				P<0.0001
					Preoperative IABP		HR=17[i]				P<0.0001
					Perioperative MI		HR=5.4[i]				P<0.0001

a: death, myocardial infarction, or cardiac surgical procedures

b: overall mortality rate

c: overall mortality rate, calculated from the text

d: the p-value was obtained from a chi-squared test.

e: preoperative measurements

f: cardiac mortality rate

h: there was no mortality rate reported, multivariate analysis showed that female was a predictor of late death.

Study	Population (N)	Age years mean±SD	Male (%)	LVEF (%)	Risk factor	Mean survival time, in months (range)	Event rate 1 year (%)	Event rate 2 year (%)	Event rate 3 year (%)	Event rate 5 year (%)	P-value
I: hazard ratio for late cardiac deaths CABG: coronary artery bypass grafting CEPB: Carpentier-Edwards pericardial bioprosthesis NS: not significant AVR: aortic valve replacement IABP: intraaortic balloon pump MI: myocardial infarction HR: hazard ratio											

7 References

1 Road Safety Research Report No. 67 Expert Consensus Workshop: Driving Safety and Cardiac Ischaemia, 7-8 July 2005. http://www.*dft.gov.uk/pgr/roadsafety/research/rsrr/theme6/expertconsensusworkshopdrivi4790?version=1,*Accessed Feb. 2007.

2 Understanding Systematic Reviews of Research on Effectiveness, CRD's Guidance for those Carrying Out or Commissioning Reviews, CRD Report Number 4 (2nd Edition). http://www.*york.ac.uk/inst/crd/report4.htm* 2001.

3 Mahenthiran J, Bangalore S, Yao SS, Chaudhry FA. Comparison of prognostic value of stress echocardiography versus stress electrocardiography in patients with suspected coronary artery disease. *Am J Cardiol* 2005; **96**(5):628-634.

4 Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002; **346**(11):793-801.

5 Shaw LJ, Hendel R, Borges-Neto S, Lauer MS, Alazraki N, Burnette J, *et al*. Prognostic value of normal exercise and adenosine (99m)Tc-tetrofosmin SPECT imaging: results from the multicenter registry of 4,728 patients.[erratum appears in J Nucl Med. 2003 Apr;44(4):648]. *Journal of Nuclear Medicine* 2003; **44**(2):134-139.

6 Vivekananthan DP, Blackstone EH, Pothier CE, Lauer MS, Vivekananthan DP, Blackstone EH, *et al*. Heart rate recovery after exercise is a predictor of mortality, independent of the angiographic severity of coronary disease. *Journal of the American College of Cardiology* 2003; **42**(5):831-838.

7 Watanabe J, Thamilarasan M, Blackstone EH, Thomas JD, Lauer MS, Watanabe J, *et al*. Heart rate recovery immediately after treadmill exercise and left ventricular systolic dysfunction as predictors of mortality: the case of stress echocardiography. *Circulation* 2001; **104**(16):1911-1916.

8 D'Andrea A, Severino S, Caso P, De SL, Liccardo B, Forni A, *et al*. Prognostic value of pharmacological stress echocardiography in diabetic patients. *European Journal of Echocardiography* 2003; **4**(3):202-208.

9 Nishiyama S, Iwase T, Ishiwata S, Komiyama N, Kobayashi T, Naruse Y, *et al*. Comparison of long-term efficacy of medical treatment versus coronary artery bypass grafting (CABG) in multivessel coronary artery disease. *Japanese Heart Journal* 1995; **36**(6):709-717.

10 Supino PG, Wallis JB, Chlouverakis G, Borer JS, Supino PG, Wallis JB, *et al*. Risk stratification in the elderly patient after coronary artery bypass grafting: the prognostic value of radionuclide cineangiography. *Journal of Nuclear Cardiology* 1994; **1**(2 Pt 1):159-170.

11 Talwalkar NG, Damus PS, Durban LH, Hartstein ML, Taylor JR, Weisz D, *et al*. Outcome of isolated coronary artery bypass surgery in octogenarians. *Journal of Cardiac Surgery* 1996; **11**(3):172-179.

12 Appoo J, Norris C, Merali S, Graham MM, Koshal A, Knudtson ML, *et al*. Long-term outcome of isolated coronary artery bypass surgery in patients with severe left ventricular dysfunction. *Circulation* 2004; **110**(11 Suppl 1):II13-II17.

13 Formica F, Greco P, Colagrande L, Martino A, Corti F, Ferro O, *et al*. Right gastroepiploic artery graft: Long-term clinical follow-up in 271 patients - Experience of a single center. *Journal of Cardiac Surgery* 2006; **21**(6):539-544.

14 Luciani N, Nasso G, Gaudino M, Abbate A, Glieca F, Alessandrini F, *et al*. Coronary artery bypass grafting in type II diabetic patients: a comparison between insulin-dependent and non-insulin-dependent patients at short- and mid-term follow-up. *Annals of Thoracic Surgery* 2003; **76**(4):1149-1154.

15 Hakala T, Pitkanen O, Halonen P, Mustonen J, Turpeinen A, Hippelainen M. Early and late outcome after coronary artery bypass surgery in diabetic patients. *Scandinavian Cardiovascular Journal* 2005; **39**(3):177-181.

16 Ono T, Kobayashi J, Sasako Y, Bando K, Tagusari O, Niwaya K, *et al*. The impact of diabetic retinopathy on long-term outcome following coronary artery bypass graft surgery. *Journal of the American College of Cardiology* 2002; **40**(3):428-436.

17 Mistiaen WP, Van CP, Muylaert P, Van HM, Sys SU, Harrisson F, *et al*. Determinants of survival after aortic valve replacement as treatment for symptomatic aortic valve disease in the elderly. *Journal of Heart Valve Disease* 2001; **10**(3):354-360.

18 Myler RK, Shaw RE, Stertzer SH, Zapolanski A, Zipkin R, Murphy MC, *et al*. Triple vessel revascularization: coronary angioplasty versus coronary artery bypass surgery: initial results and five-year follow-up. Comparative costs and loss of working days and wages. *Journal of Invasive Cardiology* 1994; **6**(4):125-135.

8 Appendices

8.1 Appendix 1 – Details of Request

ARIF REQUEST FORM

Date of request	6/12/2006
Lead Medical Adviser issuing request	Name – Dr Jonathan Hanley, Secretary to the Cardiac Panel
Contact details	Drivers Medical Group DVLA Sandringham Park Swansea Vale Llansamlet Swansea SA7 0AA [redacted] Email: [redacted]

1. Without worrying about the structure of the question, state in full the nature and context of the problem.

1. What proportion of those undertaking exercise testing, can complete 3 stages of the standard Bruce Protocol (or equivalent) with an LVEF of less than 40%.

2. What additional factors identify those who have undergone Coronary Artery Bypass Grafting (CABG) are at an increased risk of a further sudden cardiac event post procedure assuming that their LVEF post procedure (3 months at least) is 40% or more. i.e. are we looking for a group of person who remain at excess risk despite surgery who therefore will need closer scrutiny than the usual 3 year interval assessment,

2. Please give a background to the question. Why has DMG raised this problem?

Impaired LVEF in its own right is associated with sudden cardiac events causing incapacity. The critical tipping point is 40%. Below this level incapacitating events increase exponentially. A documented LVEF of <40% debars Group 2 licensing. (Panel opinion held since at least 1988).

Exercise testing (must complete 3 stages of standard Bruce protocol, equivalent to 10 mets) is used to determine Group 2 licensing fitness when there is a history of ischaemic heart disease. Routine use of echocardiography to measure LVEF does not occur. Whilst it is unlikely that many people could achieve the exercise test requirements with an LVEF of <40% there is concern and anecdotal case evidence that some have managed the exercise test requirement despite impaired LVEF (<40%) who therefore remain at high risk for the reasons described in the paragraph above.

3. Giving references where appropriate, briefly detail the sources you have used to obtain background information on the *options* and *issues,* which might be important for the problems, you describe.

Chapter 2 Cardiovascular Disorders – At a Glance to the current Medical Standards of Fitness to Drive August 2006

4. Please give name and contact details of any expert or clinical contact e.g. relevant Panel Chairman/expert Panel member.

Dr H Swanton (Chairman)
MB Bchir MRCP Ma MS FRCP FESC
Consultant Cardiologist
The Heart Hospital
Westmoreland Street
London
W1G 8PH
[redacted]

Dr A Kelion
DM MRCP
Consultant Cardiologist
Harefield Hospital
Hill End Road
Harefiled
Middlesex
UB9 6JH
[redacted]

Mr G E Venn
MB BS MS FRCS FICS FETCS
Cariothoracic Surgeon
Guy's & St Thomas Hospital
Cardiothoracic Centre
Lambeth Palace Road
London
SE1 7EH
[redacted]

The above-named would be the main contact, but a list of the other panel members is attached for completeness.

5. What is the nature of the target population of the issue detailed above? Eg. age profile, vocational drivers, young drivers, other co-morbid features.

Group 2 drivers

6. What are the outcomes you consider particularly important in relation to the question posed? What decisions rest on these outcomes?

1. Can DVLA be confident that exercise testing of those with a history of I.H.D. effectively excludes those with LVEF<40% if 3 stages of the Standard Bruce Protocol are completed without disbarring aspects appearing during test or recovery periods? 2. Can we identify (CABG cases) where there may be a group of significantly higher risk cases that may need closer scrutiny than the usual 3 year licensing period?

7. What is the latest date that an ARIF response would be of value | 29 / 2 |

Please either:

Fax this form to: 0121 414 7878 marking FAO ARIF

E-mail as a word document or pdf attachment to: [redacted]

Post to: - Dr David Moore
Senior Research Reviewer and Analyst
Aggressive Research Intelligence Facility
West Midlands Health Technology Assessment Collaboration
Department of Public Health
University of Birmingham
Edgbaston
Birmingham
B15 2TT

Please ring 0121 414 3166 or 6769 if you have any queries, or you want to check the progress with your request.

8.2 Appendix 2 – Search strategies

8.2.1 ARIF Reviews Protocol

SEARCH PROTOCOL FOR ARIF ENQUIRIES

(Oct 2006)

In the first instance the focus of ARIF's response to requests is to identify systematic reviews of research. The following will generally be searched, with the addition of any specialist sources as appropriate to the request.

1. Cochrane Library

- Cochrane Reviews
- Database of Abstracts of Reviews of Effects (DARE)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Health Technology Assessment (HTA) database

2. ARIF Database

An in-house database of reviews compiled by scanning current journals and appropriate WWW sites. Many reviews produced by the organisations listed below are included.

3. NHS CRD

- DARE
- Health Technology Assessment Database
- Completed and ongoing CRD reviews

4. Health Technology Assessments and Evidence Based guidelines

- NICE appraisals and work plans for TARs, Interventional Procedures and Guidelines programmes, Public Health excellence
- SBU – Swedish Council on Technology Assessment in Health Care
- NHS Coordinating Centre for Health Technology Assessments
- Canadian Agency for Drugs and Technologies in Health
- New Zealand Health Technology Assessment
- STEER Reports (no longer published)
- Agency for Healthcare Research and Quality (AHRQ)
- Alberta Heritage Foundation
- McGill Medicine Technology Assessment Unit of MUHC (McGill University Health Centre)
- Monash reports – Centre for Clinical Effectiveness, Monash University
- US Department of Veterans Affairs
- NHS QIS (Quality Improvement Scotland)
- SIGN (Scottish Intercollegiate Guidelines Network)

5. Clinical Evidence

6. Bandolier

7. National Horizon Scanning Centre

8. TRIP Database

9. Bibliographic Databases

- Medline – systematic reviews
- Embase – systematic reviews
- Other specialist databases

10. Contacts

- Cochrane Collaboration (via Cochrane Library)
- Regional experts, especially Pharmacy Prescribing Unit, Keele University (& MTRAC) and West Midlands Drug Information Service for any enquiry involving drug products.

8.2.2 Primary Studies Search Strategies

Question 1

Source – Cochrane Library 2007 Issue 1 (Wiley Internet version)

#1 bruce next protocol*
150

#2 bruce next treadmill
20

#3 MeSH descriptor Exercise Test explode all trees
4476

#4 MeSH descriptor Exercise Tolerance explode all trees
826

#5 exercise next stress next test*
232

#6 #1 OR #2 OR #3 OR #4 OR #5)
5146

#7 left next ventricular next ejection next fraction
1636

#8 lvef
530

#9 MeSH descriptor Ventricular Function, Left explode all trees
1271

#10 MeSH descriptor Ventricular Dysfunction, Left explode all trees
943

#11 MeSH descriptor Cardiac Output, this term only
1354

#12(#7 OR #8 OR #9 OR #10 OR #11)
4595

#13 (#6 AND #12)
549

#14 stress next echocardiography
153

#15 myocardial next perfusion next scintigraphy
37

#16 MeSH descriptor Echocardiography, Stress, this term only
48

#17 (#14 OR #15 OR #16)
206

#18 (#13 AND #17)
26

Source - Ovid MEDLINE(R) 1950 to January Week 3 2007

1 bruce protocol.mp. (584)
2 bruce treadmill.mp. (76)
3 exercise stress test$.mp. (1623)
4 exercise test/ (35882)
5 exercise tolerance/ (3632)
6 or/1-5 (38594)
7 limit 6 to "diagnosis (optimized)" (5706)
8 limit 7 to "reviews (optimized)" (583)
9 limit 7 to "reviews (specificity)" (32)
10 exp echocardiography/ (68235)
11 myocardial perfusion scintigraphy.mp. (455)
12 stress echocardiography.mp. (2026)
13 echocardiography,stress/ (957)
14 or/10-13 (68853)
15 6 and 14 (3957)
16 limit 15 to "diagnosis (optimized)" (1209)
17 limit 16 to "reviews (specificity)" (18)
18 limit 15 to "reviews (optimized)" (512)
19 limit 15 to "reviews (specificity)" (20)
20 9 or 17 or 19 (34)

Source - Ovid MEDLINE(R) 1950 to January Week 3 2007

1 bruce protocol.mp. (584)
2 bruce treadmill.mp. (76)
3 exercise stress test$.mp. (1623)
4 exercise test/ (35882)
5 exercise tolerance/ (3632)
6 or/1-5 (38594)
7 limit 6 to "diagnosis (optimized)" (5706)
8 limit 6 to "diagnosis (specificity)" (1727)
9 (left ventricular ejection fraction or lvef).mp. (10083)
10 ventricular function, left/ (17194)
11 ventricular dysfunction, left/ (10111)
12 cardiac output/ (33995)
13 or/9-12 (65250)
14 6 and 13 (3983)
15 limit 14 to "diagnosis (optimized)" (677)
16 limit 14 to "diagnosis (specificity)" (194)
17 stress echocardiography.mp. (2026)
18 echocardiography, stress/ (957)

19 myocardial perfusion scintigraphy.mp. (455)
20 or/17-19 (2828)
21 14 and 20 (231)
22 limit 21 to "diagnosis (optimized)" (103)
23 limit 22 to humans (102)

Source - EMBASE (Ovid) 1980 to 2007 Week 04

1 bruce protocol.mp. (575)
2 bruce treadmill.mp. (88)
3 exercise stress test$.mp. (1487)
4 exercise test/ (13606)
5 exercise tolerance/ (4478)
6 or/1-5 (18437)
7 limit 6 to "diagnosis (optimized)" (2658)
8 limit 7 to "reviews (2 or more terms high specificity)" (22)
9 exp echocardiography/ (72058)
10 myocardial perfusion scintigraphy.mp. (464)
11 stress echocardiography.mp. (2824)
12 or/9-11 (72613)
13 6 and 12 (2572)
14 limit 13 to "diagnosis (optimized)" (710)
15 limit 14 to "reviews (2 or more terms high specificity)" (11)
16 limit 13 to "reviews (2 or more terms high specificity)" (16)
17 8 or 15 or 16 (27)
18 limit 17 to human (26)

Question 2

Source – Cochrane Library 2007 Issue 1 (Wiley internet version)

#1 cabg
1444

#2
coronary next artery next bypass
4874

#3
MeSH descriptor Coronary Artery Bypass, this term only
3393

#4
(#1 OR #2 OR #3)
5024

#5
left next ventricular next ejection next fraction
1636

#6
lvef
530

#7
MeSH descriptor Ventricular Function, Left, this term only
1271

#8
MeSH descriptor Ventricular Dysfunction, Left, this term only
943

#9
(#5 OR #6 OR #7 OR #8)
3366

#10
(#4 AND #9)
306

#11
cohort or prognostic or prognosis
22582

#12
(#10 AND #11)
46

Source - Ovid MEDLINE(R) 1950 to January Week 4 2007

1 cabg.mp. (6946)
2 coronary artery bypass.mp. (36242)
3 Coronary Artery Bypass/ (30987)
4 or/1-3 (36799)
5 (left ventricular ejection fraction or lvef).mp. (10105)
6 ventricular function, left/ (17208)
7 ventricular dysfunction, left/ (10129)
8 cardiac output/ (34010)
9 or/5-8 (65306)
10 4 and 9 (2735)
11 limit 10 to "prognosis (specificity)" (267)
12 limit 11 to humans (267)

Source – EMBASE (Ovid) 1980 to 2007 Week 05

1 cabg.mp. (6350)
2 coronary artery bypass.mp. (31646)
3 coronary artery bypass graft/ (21993)
4 or/1-3 (32089)
5 (left ventricular ejection fraction or lvef).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (9798)
6 heart left ventricle function/ (11709)
7 or/5-6 (20188)
8 4 and 7 (1598)
9 limit 8 to (human and "prognosis (specificity)") (487)
10 limit 9 to (human and "reviews (2 or more terms min difference)") (39)
11 limit 9 to yr="2004 - 2007" (99)