Title:	**Second-generation contrast agents for use in patients with suboptimal echocardiograms**
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Aim
To assess the safety, effectiveness and cost-effectiveness of echocardiography with second-generation contrast agents in (a) patients requiring assessment of ventricular function, ventricular morphology or intracardiac mass (b) patients being assessed for ischaemic heart disease using stress echocardiography, and (c) patients requiring Doppler evaluation of the left heart, who have had prior suboptimal echocardiograms.

Results and Conclusions
Safety
A total of 27 studies reported on the safety of echocardiography using second-generation contrast agents (Optison or Definity).Thirteen of these studies reported no adverse events. A total of 4841 adverse events were reported in the remaining 14 studies, with the rate of adverse events ranging from 0.03 per cent to 87.1 per cent. Common complications included arrhythmias, atrial fibrillation, headache, back pain, chest pain, nausea and vomiting and shortness of breath. Eight studies compared the safety of echocardiography using second-generation contrast agents with that of noncontrast echocardiography. The rate of adverse events appeared similar between the contrast and noncontrast groups in all studies, and this was confirmed statistically in five studies.

Effectiveness
Effectiveness of echocardiography with contrast compared with echocardiography without contrast
Indication 1 – Patients requiring assessment of ventricular function, ventricular morphology or intracardiac mass
A total of 13 studies were identified. Most studies were level IV studies of diagnostic yield, while one study was a prospective cohort, cross-classified (level III-1) study.

The administration of contrast was shown to significantly reduce the need for additional diagnostic procedures, specifically nuclear imaging or transoesophageal echocardiography (TOE). In addition, contrast administration significantly altered patients' drug regimens, including the addition or discontinuation of haemodynamically active drugs and the addition or cessation of anticoagulants.

Two studies reported that contrast administration increased the reproducibility of echocardiographic assessment of left ventricular function, with one of these studies reporting a significant improvement with contrast administration. Similarly, one study reported that contrast administration significantly increased the accuracy of absolute left ventricular volume determination, when electron beam computed tomography (EBCT) was used as the reference standard.

One study reported that contrast administration did aid in the diagnosis of apical hypertrophic cardiomyopathy in patients with suggestive electrocardiography and SPECT examinations, but nondiagnostic baseline transthoracic echocardiograms (TTEs).

Five studies evaluated the rate of conversion from nondiagnostic to diagnostic studies following contrast administration, and reported that diagnostic yield ranged from 56 per cent to 100 per cent. Four of these studies reported a significant increase in the proportion of diagnostic studies following contrast administration.

Eight studies demonstrated an improvement in endocardial border visualisation or delineation following contrast administration, and in seven of these studies the improvement was significant. Similarly, three

studies that evaluated left ventricular cavity enhancement or opacification demonstrated a significant improvement following contrast administration.

Indication 2 – Patients being assessed for ischaemic heart disease using stress echocardiography
A total of 12 studies were identified. Most studies were prospective cohort, cross-classified diagnostic studies (level III-2), while five studies were level IV studies of diagnostic yield.

One study demonstrated that among patients with suboptimal baseline images, 53 per cent subsequently undergo an additional nuclear stress test, compared with 3 per cent had they received contrast enhancement.

With the addition of contrast, the sensitivity (proportion of people with the disease who have a positive test result) of echocardiographic studies improved in all but one study, while the specificity (proportion of people without disease who have a negative test result) was similar or slightly reduced. Other outcomes of diagnostic yield, where provided, also showed an improvement in image quality in favour of contrast echocardiography. In most, but not all cases, this was statistically significant.

Indication 3 – Patients requiring Doppler evaluation of the left heart
No studies were identified for this indication.

Effectiveness of echocardiography with contrast compared with alternative investigations
Indication 1 – Patients requiring assessment of ventricular function, ventricular morphology or intracardiac mass
No studies were identified for this indication.

Indication 2 – Patients being assessed for ischaemic heart disease using stress echocardiography
Two prospective cohort, cross classified diagnostic studies (level III-2) comparing contrast echocardiography with nuclear myocardial perfusion imaging were identified.

Both studies reported diagnostic accuracy data; however, each study used a different stenosis threshold for diagnosis of ischaemia. Good agreement was observed between SPECT and wall motion analysis using stress echocardiography with contrast in both studies; however, the statistical significance of these relationships was not reported. The reproducibility of contrast echocardiography for the assessment of patients with coronary artery disease was compared with SPECT in one study, which reported lower interobserver and intraobserver variability for contrast echocardiography. However, the study did not report the statistical significance of these observations.

Indication 3 – Patients requiring Doppler evaluation of the left heart
No studies were identified for this indication.

Cost-effectiveness
The cost-effectiveness analysis considered the procedural and downstream investigation cost of using contrast following a suboptimal echocardiogram compared with not using contrast. While the use of contrast increased the time commitment required to complete echocardiography, and the cost of the investigation, it led to a substantial cost saving as a result of reduced downstream costs, such as gated cardiac blood pool studies, myocardial perfusion studies and transoesophegeal echocardiography. Considering costs that accrue to the Medicare Benefits Schedule (MBS), the rest of the healthcare system, and the patient through co-payments, the cost offsets associated with the use of contrast agent exceed the additional cost incurred by using it. The cost saving for stress echocardiography was estimated to be $12.38 million per year. This figure breaks down into a saving of $10.35 million to the MBS, $2.1 million to patients, and a positive cost of $68,165 to the non-MBS health sector. For the rest echocardiogram and Doppler evaluation, the cost saving was $28.22 million per year. This was subdivided into savings to the MBS of $19.44 million, to patients of $9.16 million, and a positive cost of $386,978 for the health care system. These results assume no leakage to patients without suboptimal echocardiography.

Methods
The evidence regarding the use of second-generation contrast agents in patients who have had prior suboptimal echocardiograms was systematically assessed. For studies assessing the effectiveness of echocardiography with contrast compared with echocardiography without contrast, PubMed was searched from January 2000 to July 2009. For studies assessing the effectiveness of echocardiography with contrast compared with alternative investigations, EMBASE, AustHealth, Current Contents, CINAHL, PubMed and the Science Citation Index were searched for relevant literature from inception of the databases to March 2010. Studies were included in the review using pre-determined PICO selection criteria and reasons for

exclusion were documented. The quality of studies was assessed, data were extracted in a standardised manner, and results were reported narratively.