MSAC Application 1713

Cardiac MRI in the diagnosis of myocarditis

PICO Confirmation

Summary of PICO/PPICO criteria to define question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Table 1 PICO for cardiac MRI in the diagnosis of myocarditis: PICO Set 1

Component	Description
Test population	There are two test populations for this application. Population 1: patients with signs and symptoms of acute onset cardiomyopathy (acute heart failure and/or arrythmia) suggestive of acute myocarditis Population 2: patients presenting with signs and symptoms of acute coronary syndrome with an intermediate risk of obstructive coronary artery disease, or suspected myocarditis
Prior tests	Population 1: initial testing and standard investigation for signs and symptoms of heart failure and cardiomyopathy, including blood test (e.g. ESR, CRP, troponin), ECG, chest X-ray, transthoracic echocardiography (TTE) Population 2: initial testing and standard investigation for signs and symptoms of suspected acute coronary syndrome (ACS) (ECG, troponin, chest X-ray)
Intervention	Cardiac magnetic resonance imaging (CMR) using gadolinium-based contrast
Comparator/s	Population 1: standard management (e.g. antifailure Rx, circulatory support, antiarrhythmic Rx) with/without endomyocardial biopsy (EMB) when clinically indicated. Population 2: standard management of intermediate-risk ACS including CTCA / ICA to exclude obstructive coronary artery disease (CAD) ±TTE
Reference standard	EMB
Outcomes (to be reported separately for each population when possible)	<u>Safety</u> Rates of inappropriate therapy Adverse events arising from the intervention and comparator procedures (e.g. contrast adverse reaction, other adverse events arising from cardiac MRI, claustrophobia requiring the administration of sedation or general anaesthetic, exposure to ionising radiation) <u>Efficacy/effectiveness</u> Cardiac MRI performance outcomes: • sensitivity and specificity • positive likelihood ratio, negative likelihood ratio • receiver operating characteristic (ROC) curves • number needed to diagnose or refute myocarditis • diagnostic yield Patient management outcomes: • diagnostic utility – for each population, confirmation of presumed diagnosis of myocarditis or ACS mimic) • change in clinical management • prognostic utility (for each population) – informed change in prognosis without change in treatment* • predictive utility - change in treatment pathway (initiated, ceased, modified, avoided) o commencement of appropriate targeted or non-targeted treatment • need for subsequent EMB (the need to have a repeat EMB, the need for EMB after cardiac MRI) Health outcomes:

	• cardiovascular-related morbidity (including chronic heart failure therapy, hospitalisations for heart failure, need for device-related therapy [cardiac resynchronisation therapy {CRT} / implantable cardioverter defibrillator {ICD}]), cardiac transplantation. • cardiovascular-related mortality • all-cause mortality • health-related quality of life Non-health outcomes: • The value of knowing, including: ○ impact on patient behaviour (e.g., avoid / resume exercise) <u>Healthcare system</u> • costs associated with the intervention and comparator procedures including costs of appointments, gadolinium-based contrast administration, blood test, need for anaesthetic • costs associated with adverse events for the intervention and comparator • incremental cost-effectiveness ratio • total Australian Government healthcare costs
Assessment questions	What is the safety, effectiveness and cost-effectiveness of diagnosis with cardiac MRI versus standard management with or without EMB in patients with suspected acute or fulminant myocarditis presenting with acute heart failure and /or arrythmia? What is the safety, effectiveness and cost-effectiveness of diagnosis with cardiac MRI versus standard management standard management with or without EMB after exclusion of obstructive CAD in patients with suspected myocarditis presenting with signs and symptoms of acute coronary syndrome?

** PASC considered that prognostic utility could also be categorised as a non-health outcome (e.g. value in knowing).*

Background

This PICO was initially considered by the PICO Advisory Subcommittee (PASC) in August 2022. Following its first consideration, several outstanding issues were identified as requiring resolution before a ratified PICO could be endorsed by the Committee. These were:

- the proposed population (in particular Population 2) should be further refined
  - that the pre-test probabilities of CAD (i.e., high, low or intermediate) could be used to identify the patient population who would benefit from CMR
  - it could target the population in whom unresolved symptoms warrant further investigations and management
  - population (and MBS item descriptor) should be more specific on patient eligibility criteria to cardiac MRI, such as reflecting the clinical pathways, or findings from relevant prior tests.

In addition, due to the clarifications needed around the Population 2 including the need to stratify the population for pre-test likelihood for obstructive CAD, the comparator(s) for this population (and any defined subgroups) and algorithms may be subject to change.

For these reasons, PASC determined these issues could be re-considered at the subsequent December 2022 PASC meeting.

Purpose of application

An application requesting public funding of cardiac Magnetic Resonance Imaging (MRI) in the diagnosis of myocarditis was received from the Cardiac Society of Australia and New Zealand (CSANZ) by the Department of Health.

Cardiac MRI is a painless, non-invasive imaging technique that uses radio waves, magnets and computers to evaluate the structure and function of the heart and blood vessels without risk of exposure to ionising radiation and nephrotoxic contrast media.

Cardiac MRI can measure multiple aspects of the heart plus vascular structure and function in one examination. This includes measurement of ventricular volumes and myocardial mass, quantification of flow across heart valves, assessment of myocardial structure, assistance in the diagnosis of cardiac masses, assessment of scars, imaging of aorta and great vessels, imaging of paediatric and adult congenital abnormalities, and imaging of the proximal coronary arteries.

Cardiac MRI is widely available and accessible in Europe (Bruder et al., 2013), the UK (Keenan et al., 2021) and the USA (Goldfarb and Weber, 2021). One of the most frequent indications for the use of cardiac MRI is suspected myocarditis, which represents about one third of all referrals in Europe (Friedrich et al., 2009, Kotanidis et al., 2018). According to the position paper published in 2020 by the Society for Cardiovascular Magnetic Resonance, cardiac MRI is considered to be the non-invasive gold standard in quantifying biventricular volume, myocardial mass and regional or global systolic function (Leiner et al., 2020). Guidelines from the European Society of Cardiology (ESC), the National Heart Foundation of Australia and CSANZ recommended the use of cardiac MRI in diagnosing acute myocarditis. There is emerging evidence to support the use of cardiac MRI in diagnosing myocarditis. In Australia, the use of cardiac MRI for myocarditis is not funded by MBS. At present, a Medicare rebate for cardiac MRI can be accessed for conditions such as congenital heart disease, aortic disease, arrhythmogenic right ventricular cardiomyopathy (ARVC; and families of ARVC patients) and for the assessment of cardiac masses. A temporary MBS item (63399) was listed to aid in diagnosing myocarditis associated with mRNA COVID-19 vaccination, which is currently scheduled to end after 31 December 2022. It is proposed that the temporary MBS item (63399) be expanded to include the use of cardiac MRI for more accurate diagnosis of patients with suspected myocarditis, regardless of the association with mRNA COVID-19 vaccination.

In 2017, as part of MSAC Application 1432, the use of cardiac MRI in the diagnosis of myocarditis was considered in a subset of patients (population 5). Due to the limited evidence presented to the committee, MSAC was unable to determine the benefit of cardiac MRI in population 5 (patients with troponin-positive chest pain, electrocardiographic changes suspicious of acute coronary syndrome, and no culprit lesion identified on coronary angiography). MSAC noted that the result of the cost-effectiveness analysis in population 5 was highly uncertain, difficult to interpret and may not capture all relevant patient outcomes. MSAC noted that a more comprehensive cost-effectiveness analysis (more inputs and longer time horizon) would be needed to value cardiac MRI. The primary use of cardiac MRI in all populations in this application was as an adjunct diagnostic tool in conjunction with echocardiography, ECG and clinical examination.

PASC agreed with the purpose of application but noted that the test purpose related to the COVID-19 vaccination (diagnosis of mRNA vaccination-related myocarditis) is encompassed by the major claim of this application for population 1. Therefore, these secondary outcomes have been amalgamated in this application in line with PASC's advice.

PICO criteria

Population

At its August 2022 meeting, PASC advised that further work was needed to define the patient populations (and MBS item descriptors), in particular to provide clarity around population 2 (and the subsequent appropriate comparator and clinical management algorithms. PASC also queried whether the patient population could be more targeted to the duration of patient symptoms- given that most patients have a favourable prognosis following myocarditis in order to target the patient population where unresolved symptoms warrant further investigations and management.

In addition, PASC considered that the population (and MBS item descriptor) should be more specific on patient eligibility criteria to cardiac MRI, such as reflecting the clinical pathways, or findings from relevant prior tests.

Definition of the condition

Myocarditis is defined clinically as the inflammation of the myocardium. It is characterised by the presence of inflammatory infiltrate in combination with degenerative and/or necrotic changes to adjacent cardiomyocytes in the absence of ischemia (Ali et al., 2022, Elsanhoury et al., 2021, Caforio et al., 2017). Myocarditis may result from infectious and non-infectious causes (Sagar et al., 2012). In 50% of cases, no specific cause can be identified (Al-Akchar and Kiel, 2021). Myocarditis can occur as a response to direct viral infections (including COVID-19) or as a post-viral immune-mediated reaction. It can also occur following bacterial fungal, protozoal or parasitic infections. Additionally, myocarditis can be attributed to non-infectious causes, such as a complication of an autoimmune disorder, or as a consequence of drug reactions or environmental toxins (Takeuchi et al., 2018). In addition to coronavirus infection, receiving mRNA-based COVID-19 vaccines has been reported to increase the risk of myocarditis, particularly among adolescents and young males (Siripanthong et al., 2020, Oster et al., 2022). A summary of the array of aetiologies associated with myocarditis is presented in Table 2.

Table 2 Aetiologies of myocarditis

Infectious	Toxicity or Hypersensitivity reaction	Autoimmunity
Viral Adenovirus, arborvirus, Chikungunya virus, Cytomegalovirus, echovirus, Enterovirus (Coxsackie B), Epstein-Barr virus, Flavivirus (dengue fever and yellow fever), hepatitis B virus, hepatitis C virus, herpes viruses (human herpesvirus-6), HIV/AIDS, influenza A and B viruses, Parvovirus (parvovirus B-19), mumps virus, poliovirus, rabies virus, respiratory syncytial virus, rubeola virus, rubella virus, varicella virus, variola virus (smallpox), SARS-CoV-2 *Bacterial* *Burkholderia pseudomallei* (melioidosis), Brucella, Chlamydia (especially *Chlamydia pneumoniae* and *Chlamydia psittaci*), *Corynebacterium diphtheriae* (diphtheria), *Francisella tularensis* (tularemia), *Haemophilus influenzae*, Gonococcus, Clostridium, *Legionella pneumophila* (Legionnaire disease), *Mycobacterium tuberculosis*, *Neisseria meningitidis*, Salmonella, Staphylococcus, Streptococcus A (rheumatic fever), *Streptococcus pneumoniae*, syphilis, tetanus, Vibrio *cholerae* *Rickettsial* *Coxiella burnetii* (Q fever), *Rickettsia tsutsugamuschi* *Fungal* Aspergillus, Actinomyces, Blastomyces, Candida, Coccidioides, Cryptococcus, Histoplasma, Mucormycoses, Nocardia, Sporothrix *Protozoal* *Trypanosoma cruzi, Toxoplasma gondii,* Entamoeba, Leishmania *Parasitic* *Trichinella spiralis, Echinococcus granulosus, Taenia solium*	*Drugs* Aminophylline, amphetamines, anthracyclines, catecholamines, chloramphenicol, cocaine, cyclophosphamide, doxorubicin, ethanol, 5-flurouracil, imatimib mesylate, interleukin-2, methysergide, phenytoin, trastuzumab, zidovudine, immune checkpoint inhibitors, mRNA-based COVID-19 vaccines *Environmental* Arsenic, carbon monoxide, copper, iron, lead Spirochetal: Borrelia burgdorferi (Lyme disease), Borrelia recurrentis (relapsing fever), Leptospira, Treponema pallidum (syphilis) *Hypersensitivity reactions* Drugs: azithromycin, benzodiazepines, clozapine, cephalosporins, dapsone, dobutamine, gefitinib, lithium, loop diuretics, methyldopa, mexiletine, nonsteroidal anti-inflammatory drugs, penicillins, phenobarbital, smallpox vaccination, streptomycin, sulfonamides, tetanus toxoid, tetracycline, thiazide diuretics, tricyclic antidepressants	Immunologic syndromes Churg-Strauss Diabetes mellitus Giant cell myocarditis Sarcoidosis Systemic lupus erythematosus Sjogren's syndrome Takayasu's arteritis Thyrotoxicosis Vasculitis Polymyositis Wegener granulomatosis

Adapted from (Blauwet and Cooper, 2010, Magnani and Dec, 2006, Golpour et al., 2021)

PASC noted that post mRNA-vaccination myocarditis is an uncommon event which predominantly affects young males and that the majority of patients have a favourable prognosis. PASC noted advice that patients with suspected myocarditis associated with COVID-19 vaccinations may not be limited to mRNA vaccines only (as per temporary item), and that other generation COVID-19 vaccines may also be associated with a risk of myocarditis, but less frequently than seen with mRNA vaccines. PASC noted that the long-term prognosis for these conditions is unknown.

Disease burden

Globally, it is estimated that the worldwide prevalence of myocarditis is 1.5 million patients, with 10-22 new cases diagnosed per 100,000 population annually (Global Burden of Disease Study 2013 Collaborators, 2015, Olejniczak et al., 2020). The clinical presentation of acute myocarditis is highly variable, ranging from asymptomatic to subtle cardiogenic shock to sudden cardiac death (Ali-Ahmed et al., 2020). The diagnosis is challenging because of the variable clinical presentation (Al-Akchar and Kiel, 2021). Evidence suggests that approximately 20% of sudden death in young adults results from myocarditis (Eckart et al., 2004). This rate

can be higher among young athletes and military recruits, as it has been proven that physical exercise increases viral titres and worsens cardiomyopathy (Maron et al., 2015, Eckart et al., 2004).

According to data from the United States Centres for Disease Control and Prevention in 2020–2021, a higher risk of myocarditis at 146 cases per 100,000 has been observed for patients infected with SARS-CoV-2 than for the general population (Boehmer et al., 2021). However, a recent study found that the risk associated with COVID-19 vaccination is far smaller than the risk directly linked to SARS-CoV-2 itself (Heymans and Cooper, 2022). This is consistent with previous studies from Israel and USA, which show that in patients receiving an mRNA COVID-19 vaccine, the incidence of mRNA-vaccine-related myocarditis ranges from 0.3–5.0 per 100,000 vaccine doses (Witberg et al., 2021, Mevorach et al., 2021, Klein et al., 2021, Montgomery et al., 2021).

In Australia, there is no detailed data on the prevalence or incidence of myocarditis in the general population. According to the Applicant, while the Australian prevalence and incidence of myocarditis considered in the Application is uncertain, it has been reasonably estimated that the overall incidence of myocarditis in the community is approximately 30 per 100,000 person years (Applicant, 2022a). In the post-vaccine population, the Therapeutic Goods Administration has reported 577 cases of myocarditis from 41 million doses of Pfizer and 97 cases from 4.5 million doses of Moderna until 5 June 2022 (Therapeutic Goods Administration, 2022). Data from the national Coronial Information System registry (2000–2016) demonstrates that myocarditis accounts for approximately 10% of sudden cardiac death in Australia, ranking behind CAD (40%) and sudden arrhythmic death syndrome (14%) (Ha et al., 2020).

Classification

The clinicopathologic classification of myocarditis is as follows (Rroku et al., 2021):

1) Acute myocarditis

Acute myocarditis is the most common type of myocarditis (65% of cases) and can be defined as a period of <1 month between symptom onset and diagnosis with increased level of high sensitivity troponin (Lampejo et al., 2021, Ammirati et al., 2020). It has a clinically more subtle onset, moderate cardiovascular compromise and incomplete recovery. Histologically, acute myocarditis is characterised by an active myocarditis defined as the presence of myocardial necrosis or degeneration (such as vacuolisation, irregular cellular outlines and cellular disruption with lymphocytes closely applied to sarcolemma)associated with the inflammatory infiltrate (Ammirati et al., 2020). It may result in cardiac dysfunction, heart failure and—infrequently—death. (Angelini et al., 2002)

2) Fulminant myocarditis

Fulminant myocarditis is a severe form of acute myocarditis. It comprises 17% of cases and has a very acute onset. The most common clinical presentation of FM are rapidly progressing severe heart failure symptoms (such as dyspnoea, peripheral oedema, chest discomfort and worsening fatigue) resulting in hemodynamic compromise and cardiogenic shock that requires treatment with inotropes or mechanical circulatory support (MCS) (Veronese et al., 2018). This can result in either a complete, spontaneous resolution or rapid deterioration and death due to severe cardiac compromise.

3) Chronic active myocarditis

Chronic active myocarditis comprises 11% of myocarditis cases. The presentation is similar to that of acute myocarditis, but it usually progresses to mild or moderate cardiac dysfunction with or without restrictive pathology. Ongoing fibrosis indicative of chronic inflammatory change is present in histological examination.

4) Chronic persistent myocarditis

Chronic persistent myocarditis affects 7% of myocarditis cases. It has a subtle onset with minimal to no cardiovascular compromise. Histologically, non-resolving active or borderline inflammatory infiltrates are present.

This PICO Confirmation will focus on acute myocarditis in which the time from symptom onset to diagnosis is relatively short.

Clinical presentation and diagnostic criteria of myocarditis

The diagnosis of myocarditis is often challenging due to the variety of aetiologies, clinical presentations and diagnostic approaches (Leone et al., 2012, Kindermann et al., 2012). During the course of myocarditis, patients can experience chest pain, palpitations, arrhythmia and acute or chronic heart failure. Symptoms and signs can range from being unnoticed to those causing permanent damage to the heart or even death. Patients presenting with mild symptoms of myocarditis with minimal ventricular dysfunction often recover without treatment (Caforio et al., 2013a). An Italian registry study showed that patients with uncomplicated acute myocarditis have a benign prognosis and are at low risk of cardiac events (Felker et al., 1999, Towbin et al., 2006, Caforio et al., 2007). However, myocarditis can be associated with a poor prognosis (e.g. progression to dilated cardiomyopathy [DCM]) and, in the most severe cases, sudden cardiac death. A considerable number (42%) of autopsy results of United States army recruits who had died suddenly showed histological evidence of myocarditis (Caforio et al., 2013a, Basso et al., 2001). Early diagnosis of myocarditis is important in preventing persistent cardiac inflammation that may lead to DCM or end stage heart failure (Biesbroek et al., 2015).

Clinical manifestations of myocarditis include: acute chest pain, pericarditic or pseudo-ischaemic chest pain; new-onset (≤3 months) or worsening of dyspnoea at rest or exercise, and/or fatigue with or without signs of left and/or right heart failure; subacute/chronic (>3 months) or worsening of dyspnoea at rest or exercise, and/or fatigue with or without signs of left and/or right heart failure; palpitation and/or unexplained arrhythmia symptoms and/or syncope and/or aborted sudden cardiac death; unexplained cardiogenic shock (Caforio et al., 2013a).

In addition to the clinical presentation, electrocardiogram (ECG), echocardiogram, cardiac biomarkers and cardiac MRI play a key complementary role in the diagnosis, treatment and follow-up of patients with myocarditis (Smith et al., 1997).

The gold standard (reference standard) for in vivo myocarditis diagnosis is histological and immunohistochemical assessment of cardiac tissue obtained by EMB (Richardson, 1996, Leone et al., 2012). Based on the Dallas criteria, the histological examination of EMB specimens provides information regarding inflammatory cells (e.g. presence, type and degree), presence of viruses, myocardial fibrosis or changes in myocardial architecture consistent with a cardiomyopathy substrate (Aretz et al., 1987, Sinagra et al., 2021, Caforio et al., 2013a). However, a viral genome may be present in the myocardium but with insufficient histologic changes to meet the Dallas criteria (Kindermann et al., 2008, Baughman, 2006). Immunohistochemical and polymerase chain reaction (PCR) analysis, in addition to histological evaluation, can confirm a definitive diagnosis of myocarditis (Caforio et al., 2013a).

Although studies and clinical trials have demonstrated the diagnostic and prognostic utility of EMB plus tests of histology and immunohistochemistry, for patients with suspected myocarditis, the invasive nature of EMB has prevented its frequent use in current clinical settings (Kindermann et al., 2008). This leads to difficulty in determining the accurate incidence of myocarditis (Leone et al., 2012).. For patients who do not undergo EMB or have non-diagnostic findings on histological and immunohistochemical tests, a diagnosis of clinically suspected myocarditis can be established, rather than a definitive diagnosis. Cardiac MRI has emerged as a useful non-invasive alternative for diagnosing myocarditis that can show the site of myocardial injury, the degree and range of myocardial inflammation, and the fibrosis repair after inflammation (Cundari et al., 2021, Polte et al., 2022)

Myocarditis should be clinically suspected when patients present with one or more of the clinical manifestations described above and one or more of the following diagnostic criteria (Caforio et al., 2013a):

- ECG/Holter/stress test features: I to III degree atrioventricular block, bundle branch block, ST/T wave change (ST elevation or non ST elevation, T wave inversion), sinus arrest, ventricular tachycardia or fibrillation and asystole, atrial fibrillation, reduced R wave height, intraventricular conduction delay (widened QRS complex), abnormal Q waves, low voltage, frequent premature beats, supraventricular tachycardia);
- myocardiocytolysis markers: elevated troponin T/I;
- functional and structural abnormalities on cardiac imaging (echocardiogram/angiography/cardiac MRI): regional wall motion or global systolic or diastolic function abnormality, with or without ventricular dilatation, with or without increased wall thickness, with or without pericardial effusion, with or without endocavitary thrombi);
- tissue characterisation by cardiac MRI: oedema and/or LGE of classical myocarditic pattern

Other features leading to suspicion of myocarditis are also considered. If the patient is asymptomatic, two or more diagnostic criteria are required (Caforio et al., 2013a). The condition is diagnosed clinically based on the typical signs and symptoms of heart failure. Patients diagnosed with heart failure may then be classified according to their left ventricular ejection fraction (LVEF) as shown in Table 3.

Table 3 Heart failure diagnostic criteria

HFrEF	HFpEF
• Symptoms & signs of heart failure and • LVEF <50%[a]	• Symptoms & signs of heart failure and • LVEF 50% and • Objective evidence of: - Relevant structural heart disease (LV hypertrophy, left atrial enlargement) and/or - Diastolic dysfunction, with high filling pressure demonstrated by any of the following: o invasive means (cardiac catheterisation) o echocardiography biomarker (elevated BNP or NT proBNP) o exercise (invasive or echocardiography)

Abbreviations: BNP: B-type natriuretic peptide, HFpEF: heart failure with preserved ejection fraction, HFrEF: heart failure with reduced ejection fraction, LV: left ventricular, LVEF: left ventricular ejection fraction, NT: N-terminal.
[a]If LVEF mildly reduced (LVEF 41–49%), additional criteria required (e.g., signs of heart failure; diastolic dysfunction with high filling pressure demonstrated by invasive means or echocardiography or biomarker testing).
Adapted from (Atherton et al., 2018)

Generally, patients with myocarditis can present with similar clinical syndromes as either acute onset cardiomyopathy (acute heart failure) or ACS. The diagnostic criteria for heart failure require patient history,

ECG, chest X-ray, transthoracic echocardiography, and blood testing (Atherton et al., 2018). Myocarditis is one of the underlying causes of heart failure.

The diagnostic criteria for ACS include elevated troponins, a clinical history consistent with myocardial ischaemia, an ECG or echocardiographic evidence of ischaemia, and evidence of coronary ischaemia on cardiac imaging (Thygesen et al., 2018). For example, a ST-segment elevation on the ECG findings can suggest a ST-elevation myocardial infarction (STEMI) subtype of ACS. For patients with troponins elevation without a culprit coronary lesion identified, a differential diagnosis including myocarditis should be considered (Chew et al., 2016).

This PICO Confirmation mainly focuses on two populations as per the proposal in the Application: patients with acute onset cardiomyopathy with suspected acute or fulminant myocarditis and patients with signs and symptoms of ACS. These populations are described in detail below.

Population 1: patients with acute onset cardiomyopathy with suspected acute myocarditis

Cardiomyopathy refers to the primary disease of the myocardium. The pathology of acute developing cardiomyopathy can result from different aetiologies, a subset of which is due to myocarditis (Saffitz and Rubin, 2019). The American Heart Association (AHA) defines cardiomyopathies as 'a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction' and 'inappropriate ventricular hypertrophy or dilatation' (Saffitz and Rubin, 2019). Therefore, patients with signs and symptoms of acute onset cardiomyopathy are considered the eligible population for testing where the underlying cause of the pathology should be determined.

Clinical presentation

Patient presentation and features

In the case of acute cardiomyopathy, patients may exhibit -symptoms such as fatigue, palpitations, shortness of breath, swelling/oedema in the legs, calves or ankles, and syncope (Olejniczak et al., 2020). Other clinical characteristics include left ventricular dysfunction, signs of fluid overload, and symptoms of acute left or right heart failure (Kurmani and Squire, 2017, Rowin et al., 2020). The patient should be admitted to the hospital for monitoring of symptoms due to variations of clinical manifestations in the initial days of disease onset.

Route for accessing care

Patients with insidious signs and symptoms of cardiomyopathy may initially present to GPs, where the aetiology, precipitating factors, severity of the clinical syndrome and initial presumptive diagnosis may be established. A patient may then be referred to a cardiologist or specialist physician to further investigate the aetiology and for guidance on disease management. Admission to ED is advised if the patient is experiencing severe difficulty in breathing, fainting or chest pains lasting longer than a few minutes.

Patients with acute onset cardiomyopathy who are experiencing severe chest pains or difficulty in breathing usually present to the emergency department (ED) requiring hospital admission for monitoring of symptoms and receipt of acute therapies.

Clinical management of suspected myocarditis

Following clinical examination of the patient, the first-line clinical investigations include: chest X-ray, ECG, transthoracic echocardiogram (TTE) and cardiac enzymes are routinely performed in the inpatient setting Table 4. Second-level tests such as EMB are frequently assessed according to international guidelines for the diagnosis of acute myocarditis for patient in this group Table 4 (Caforio et al., 2013a). Patients with suspected cardiomyopathy, including those with myocarditis, are usually referred to a specialist (cardiologist) who will order diagnostic tests to confirm the disease and plans for appropriate intervention.

Table 4 First line and second line investigation for patients with suspected acute or fulminant myocarditis

First-line clinical investigations	Second-level clinical investigations
Chest X-ray	EMB
ECG	
TTE	
Biomarkers, including cardiac enzymes (e.g. troponin)	
Cardiac MRI	

Abbreviation: ECG = electrocardiogram; EMB = endomyocardial biopsy; MRI = magnetic resonance imaging; TTE = transthoracic echocardiogram
Source: (Hazebroek et al., 2014)

For patients admitted to ED and the hospital, guideline directed medical treatment for heart failure and arrhythmias should be given to all patients with acute or fulminant myocarditis (Tschöpe et al., 2019). Aetiologies-specific treatment should depend on clinical manifestations, histology and molecular diagnosis (when applicable), and includes therapies for acute decompensated heart failure, high dose steroids and other immunological therapies. Mechanical circulation aid/support may be required (Ammirati et al., 2020). Patients who can be successfully stabilised are usually discharged from hospital after further confirmatory evaluation such as cardiac MRI or EMB. Patients with severe cardiac decompensation require ongoing investigation and further evaluation during hospitalisation. In more severe cases, advanced cardiac support such as extracorporeal membrane oxygenation, intra-aortic balloon pump, left ventricular assist device and even cardiac transplantation may be required (Miller et al., 2019, Hullin et al., 2022).

The specialist will order an imaging test or biopsy to confirm the presence of myocarditis. Patients with cardiomyopathy are usually under the care of specialist cardiologists for disease management (Charles J, 2014). Guideline-directed medical treatment for heart failure and arrhythmias should be given to all patients with acute myocarditis (Tschöpe et al., 2019).

The nonstandard or cause-specific treatment is contingent on the clinical presentation, histology and molecular diagnosis (Tschöpe et al., 2019). Treatment can be directed at the underlying aetiology if identified such as the use of corticosteroids in cases of immunomediated disease or anti-infective agents in infectious cases (Lampejo et al., 2021). However, the aetiology is not always identified or commonly of viral cause. There is no approved pathogen-directed or antiviral therapies for patients with viral myocarditis (Pollack et al., 2015).

Pathological findings

In cardiomyopathy, macroscopic examination of the heart will show ventricular chamber dilation with thickened or normal wall thickness. Valvular changes are not typical, although dilation of the valvular orifices may be present as secondary changes due to dilation of the chambers. Coronary artery anatomy is usually normal, although the presence of non-occlusive atherosclerotic plaque may be present. Thrombi can also be found on ventricles and atrial appendages (Sisakian, 2014). The development of interstitial and varying degrees of perivascular fibrosis is the most typical pattern of dilated cardiomyopathy upon histological examination. Myocardial necrosis is predominantly present at the subendocardium. In clinical examination, echocardiogram can reveal cardiac dysfunction (e.g. impaired ejection fraction). Cardiac enzymes (e.g. troponin I) are often elevated, indicating myocardial damage (Tschöpe et al., 2019).

Scope of population 1

All patients present with acute onset cardiomyopathy are considered eligible for cardiac MRI to differentiate those with myocarditis from those without myocarditis; however, the proposed population 1 in the Application may not be equivalent to patients who receive EMB for their myocarditis diagnosis in the absence of cardiac MRI. There are two reasons for this: 1) the use of EMB is recommended over cardiac MRI in certain patient populations (e.g. life-threatening arrhythmia, recurrent myocarditis, left ventricular

dysfunction progressively deteriorates within 4-5 days after onset or does not improve 4-5 days after onset [fulminant myocaridits]), and 2) patients with suspected myocarditis who are not biopsied (for various reasons) may become eligible for an unfunded cardiac MRI (Hazebroek et al., 2014).

Assessment of haemodynamic instability (see clinical management algorithms) is considered as an important initial step before proceeding to any subsequent diagnostic modality. According to NICE, haemodynamic instability is defined as perfusion failure, represented by clinical features of circulatory shock and advanced heart failure. It may also be defined as one or more out of a range vital signs such as abnormal or unstable blood pressure that results in inadequate circulation. (National Institute for Health and Care Excellence, 2014). Vital signs and surrogates of organ specific perfusion such as capillary refill time and urine output are the most commonly used clinical examination methods to evaluate haemodynamic instability. Other advance haemodynamic parameters include stroke volume (SV), cardiac output (CO), and total peripheral resistance (TPR) (Thanachartwet et al., 2016). Chest pain, confusion, low blood pressure), abnormal heart rate, loss of consciousness, restlessness, shortness of breath and cold upper of lower extremities are clinical manifestations of haemodynamic instability (Sevransky, 2009).A range of other features have also been specified in relation to the recognition and the initial management of fulminant myocarditis, including the requirement of inotropic or mechanical circulatory support, Mobitz 2 2nd-degree or higher heart block, sustained or symptomatic ventricular tachycardia or failure to respond to guideline-based medical management (Kociol et al., 2020)

There are several subgroups of patients who may require biopsy regardless of whether cardiac MRI could be performed. EMB is highly recommended in patients with suspected acute myocarditis (disease onset ≤30 days) with cardiogenic shock as presentation (Tschöpe et al., 2019). Specific forms of acute myocarditis, including giant cell myocarditis and eosinophilic myocarditis, may only be diagnosed by EMB (Tschöpe et al., 2019, Bang et al., 2021). Patients with acute cardiomyopathy complicated by hemodynamically unstable arrhythmias should be considered for early EMB to identify specific and treatable causes of heart failure (Tschöpe et al., 2019). EMB is also preferred for patients with cardiomyopathy of unknown origin (Tebbe et al., 2016). EMB should be performed in patients with clinically suspected unexplained acute myocarditis who require inotropic or mechanical circulatory support, Mobitz type 2 (≥ second degree) heart block, sustained or symptomatic ventricular tachycardia, or those who fail to respond to guideline-directed medical management within 1 to 2 weeks (Heymans et al., 2016, Bozkurt et al., 2016a). EMB may be helpful in other clinical scenarios of suspected acute myocarditis, but cardiac MRI may be considered as the initial diagnostic test to identify inflammation (Heymans and Cooper, 2022). Patients with severe and end-stage heart failure where heart transplant is considered, may also require biopsy to examine tissue types.

Due to the invasive nature of the biopsy, patients with suspected myocarditis may not all receive EMB. Based on the ESC statement in 2014, cardiac MRI is proposed as a part of the first-line investigation together with ECG, TTE and tests for blood biomarkers (e.g. serum troponin levels). Despite being considered as the definitive diagnosis of myocarditis, EMB is a part of second-level investigations (Hazebroek et al., 2014, Biesbroek et al., 2018). Patients eligible for the first line of investigation include non-EMB-indicated patients such as those with intracardiac thrombus, presence of ventricular aneurysm, severe stenosis of tricuspid, pulmonary or aortic valves, and the presence of aortic and tricuspid mechanical prosthesis (Seferović et al., 2021). Individuals with suspected SARS-CoV-2 myocarditis do not usually undergo EMB except in cases of heart block or ventricular arrhythmia (Gluckman et al., 2022). This may suggest that the population eligible for cardiac MRI for the diagnosis of suspected myocarditis may be larger than the population of patients currently indicated for EMB.

The relationship between cardiac MRI and EMB (e.g. care access and techniques) is discussed in more detail in the comparator section.

PASC noted that population 1 is defined as: patients with signs and symptoms of acute onset cardiomyopathy (acute heart failure and/or arrythmia) suggestive of acute or fulminant myocarditis. Individuals with arrhythmic myocarditis form a subset of population 1, which PASC considered need not be assessed as a distinct subgroup.

At its December 2022 meeting, PASC considered that fulminant myocarditis should be excluded from the revised population 1 as these patients would likely require EMB and be too unstable for cardiac MRI.

Population 2: patients with signs and symptoms of ACS

The second clinical presentation is in patients with signs and symptoms of ACS that have a final diagnosis of myocarditis. Myocarditis is a mimic of ACS. In this 'mimic of severe angina or myocardial infarction' the coronary arteries, which supply blood to the heart usually appear normal i.e. without evidence of stenosis (Yilmaz et al., 2008).

Clinical presentations

Patient presentation and features

It is important—and challenging—to distinguish between patients with myocarditis-related ACS mimic and those who present with acute ACS due to coronary artery disease (Mosebach et al., 2019). Clinical manifestations for acute myocarditis with ACS mimic include acute onset chest pain and/or breathlessness. Acute chest pain is the most common presenting symptom of patients with mimic of ACS presenting to Emergency. Acute myocarditis may have other clinical manifestations similar to ACS or acute coronary ischemia, such as electrocardiographic abnormalities, serum creatine kinase (CK) elevation and haemodynamic instability (Muneuchi et al., 2009).

Clinical-pathological findings

Patients with ACS can present with at least one of the following features: ongoing or repetitive chest pain despite initial ED treatment, elevated level of cardiac troponin, persistent or dynamic ECG changes of ST-segment depression ≥0.5 mm or new T-wave inversion ≥2 mm in more than two contiguous leads, transient ST-segment elevation (≥0.5 mm) in more than two contiguous leads, haemodynamic compromise, sustained ventricular tachycardia, syncope, known left ventricular systolic dysfunction (left ventricular ejection fraction <40%), prior acute myocardial infarction, percutaneous coronary intervention or prior coronary artery bypass surgery within 6 months (Chew et al., 2016).

The serum markers for myocardial damage may or may not be elevated in patients with myocarditis presenting with mimic ACS, depending on the extent of the myocardial damage (Sultan and Adnan, 2018). For patients who have chest pain with elevated myocardial enzymes and the absence of coronary artery disease, myocarditis is often the leading diagnosis. Evidence also shows that up to 81% of patients with elevated troponin and unobstructed coronary arteries are diagnosed with myocarditis (Assomull et al., 2007, Baccouche et al., 2009, Laraudogoitia Zaldumbide et al., 2009, Monney et al., 2011). Approximately 10% of patients initially diagnosed with ACS present with minimal coronary artery lesions or even a normal coronary artery on ICA (Larson et al., 2007, Yilmaz et al., 2008, Dokainish et al., 2005).

ECG changes, which can vary from nonspecific ST–T changes to ST segment elevation, are not sensitive enough for diagnosing myocarditis-related ACS mimic rather than ACS. Myocarditis can mimic a non-ST elevation ACS, which involves a partial blockage of one of the coronary arteries causing a reduced flow of oxygen-rich blood to the heart muscle. Patients with a high probability of having myocarditis usually present with diffuse ECG changes which may include sinus tachycardia and nonspecific ST/T changes or Q wave changes extending beyond the distribution of a coronary artery territory and the absence of segmental ventricular wall motion abnormalities, or the presence of global ventricular hypokinesia on cardiac echocardiogram (Sultan and Adnan, 2018, Irina et al., 2016, Vidal-Perez et al., 2019).

Route for accessing care

The initial investigation or assessment of patients with suspected myocarditis can be done in the primary care setting if the patient is not acutely or severely unwell, and if the referring practice can obtain and review the results of initial investigations (ECG, troponin, inflammatory markers, chest X-ray) within 12 hours. If this is not the case, patients should be referred to the ED immediately. Any patient presenting to a primary care physician or clinician in an outpatient setting with high-risk features such as chest pain, dyspnoea, syncope/presyncope or palpitations and suspected ACS should be referred to the ED or to a facility capable of definitive risk stratification of ACS (Chew et al., 2016).

Patients managed in the community settings or with mild symptoms should be monitored by their GP in the community every 1–2 days. Referral to ED is required if there are any concerning symptoms or abnormalities on repeat investigations.

Current Management

Acute management of patients with signs and symptoms of ACS depends on ECG changes, chest X-ray findings, blood test results and other routine clinical investigations (e.g. disease history, risk factor analysis). An initial ECG should be performed within 10 minutes of initial contact to determine occlusion of coronary arteries (acute ST elevation on ECG) causing transmural myocardial ischemia resulting in myocardial injury or necrosis. Risk assessment is undertaken to determine patient's overall ACS risk level (New South Wales Ministry of Health, 2019). According to the Applicant, the majority of patients undergo assessment for CAD, mainly with ICA or coronary CT (Applicant, 2022a).

In cases without culprit lesion identified or with low to intermediate risk of CAD, a functional test such as stress ECG or a myocardial perfusion scintigraphy (MPS) may be performed. (Shah et al., 2013, Steeds et al., 2019). MPS, as an established part of many clinical guidelines, is informative for further investigation of angina and myocardial infarction (Underwood et al., 2004). In addition, TTE may be performed to help in the evaluation of chest pain associated with myocardial ischemia, haemodynamic instability or cardiac complications (Neskovic et al., 2013). The non-ischaemic causes of the ACS mimic are then investigated. In the current diagnostic pathway for myocarditis diagnosis, ICA or cardiac CT is performed in patients with suspected CAD to rule this in/out and to diagnose myocarditis, which mimics the symptoms of CAD, by inference.

Most cases of ACS mimic due to myocarditis settle with non-steroidal anti-inflammatory drugs (NSAIDs) and/or colchicine, although in some instances myocarditis can be recurrent (Morgenstern et al., 2016). Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta blockers and diuretics might also be given to treat the underlying cause of myocarditis, based on cardiac symptoms. After hospital discharge, patients are usually monitored by their GP.

In Australia, ICA and/or cardiac CT are still recommended and commonly practiced in clinical settings for ACS investigations (as per Applicant), although these conventional tests lack sufficient specificity to make a differential diagnosis (Tipoo Sultan and Adnan, 2018, Applicant, 2022a). Additionally, there is evidence to suggest that cardiac MRI, particularly the late enhancement mapping, is a reliable criterion for early diagnosis of acute myocarditis and exclusion of CAD-associated ACS (Paule et al., 2014, Gerbaud et al., 2012, Monney et al., 2011).

Scope of the population

Patients with signs and symptoms of ACS form a significant population with many non-specific clinical presentations. These clinical presentations can indicate a wide range of underlying diseases, of which myocarditis is only one. Other conditions can also mimic ACS, such as aortic syndromes, aortic dissection and aneurysm, cardiac tamponade, cardiomyopathy, acute valvular disease and ischaemic heart disease

(Husainy et al., 2013). Due to the significant overlap in clinical features between ACS and myocarditis, the scope of the population can be difficult to characterise. Patients with a definitive diagnosis of CAD should not form part of the proposed population for this review, as cardiac MRI is not proposed to detect coronary artery disease. These patients should be excluded at the first step using appropriate diagnostic technologies. The eligible population should thus be characterised as patients with signs and symptoms of ACS with suspected myocarditis that cannot be otherwise ruled out. Therefore, patients might need further tests (e.g. stress ECG, MPS and TTE) to obtain more clinical information about the underlying disease before becoming eligible for cardiac MRI.

In addition to the issues described above, the comparator population (i.e. patients receiving ICA and cardiac CT) may not be equivalent to the cardiac MRI-eligible population because the utilisation of angiography and angioplasty is a diagnostic tool but also a means of therapeutic delivery. Coronary stents and other technologies may be delivered simultaneously while the diagnosis (for CAD) is being made. In this case, cardiac MRI may have limited value for myocarditis. It will be a clinical judgement as to whether cardiac MRI for ICA should be used for the patients with suspected but unconfirmed CAD despite results from other tests.

Of note, based on the results of prior tests (including ICA, cardiac CT, stress ECG, TTE and MPS), patients with confirmed evidence for myocarditis can be diagnosed as clinically suspected myocarditis and thus are not a part of the population 2. Patients with inconclusive or indeterminant test results or unclear myocarditis evidence will be considered.

PASC noted that the definition of population 2 is not sufficiently clear in the current PICO. PASC noted that the scope of the proposed population should be further refined to ensure the appropriate use of cardiac MRI for identifying myocarditis as the aetiology of ACS-mimic. However, the profile of patients with different CAD risk categories (e.g. high, low or intermediate pre-test risk of CAD) and the associated investigations to ascertain those risks are still unclear. It was suggested that the pre-test probabilities of CAD could be used to identify the patient population who would benefit from cardiac MRI. However, many CAD risk assessment instruments may not be appropriate for the current proposed population (e.g. paediatric or young patients who would be expected to have a low risk for CAD).

At its December 2022 Meeting, PASC noted that ACS risk status (high, intermediate and low ACS risk) may be defined by the National Heart Foundation of Australia & Cardiac Society of Australia and New Zealand guidelines (NHF-CSANZ)[1,2].

PASC noted the NHF-CSANZ guidelines were the basis for the applicant's revised population 2, defined as those presenting with intermediate-risk acute chest pain as an ACS mimic, with clinical symptoms suggestive of a cardiac cause but without any high-risk features. In this revised population, the applicant stated that acute myocarditis is the most likely diagnosis and investigation of obstructive CAD with further testing (e.g., with CTCA as a prior test) is not needed to define intermediate risk as per the NHF-CSANZ guidelines.

PASC considered that the revised population 2 was too broadly defined and at significant risk of leakage, as any patient who would otherwise meet the NHF-CSANZ criteria for low risk of ACS but who had cardiac troponin levels above the 99th centile reference limit at 0 and 2 hours after presentation would be classified

[1] Chew DP et al.; NHFA/CSANZ ACS Guideline 2016 Executive Working Group:. National Heart Foundation of Australia & Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Management of Acute Coronary Syndromes 2016. Heart Lung Circ. 2016 Sep;25(9):895-951. doi: 10.1016/j.hlc.2016.06.789.

[2] Parsonage WA et al. CSANZ Position Statement on the Evaluation of Patients Presenting With Suspected Acute Coronary Syndromes During the COVID-19 Pandemic. Heart Lung Circ. 2020 Jul;29(7):e105-e110. doi: 10.1016/j.hlc.2020.05.003.

as intermediate-risk and thus qualify for cardiac MRI. PASC noted the applicant's advice that restricting the population to only those who continued to have unresolved or persistent symptoms after a period of time would be unhelpful , since: (i) the NHF-CSANZ guidelines recommend investigation of intermediate-risk ACS patients within 30 days; and (ii) prolonging the period between symptom onset and cardiac MRI would diminish the diagnostic yield of the cardiac MRI, as resolution of inflammatory changes can be seen with cardiac MRI after 6 weeks.

The applicant acknowledged the need to define population 2 more tightly. There may be Australian data available which demonstrates that troponin-positive patients would most benefit from cardiac MRI. However, the applicant advised that setting a cut-off for troponin level (i.e. threshold) in the patient eligibility criteria for cardiac MRI would be problematic due to the variability across test assay thresholds used in Australia; despite the NHF-CSANZ recommendation above (which uses a percentile threshold which is assay agnostic).

PASC noted the applicant agreed to try and define population 2 more narrowly with the revision to be incorporated into the PICO out-of-session. PASC noted the HTA group suggested that the intention underlying the applicant's revised population 2 was broader than simply diagnosing myocarditis (as originally proposed in the application) which may overly complicate the assessment.

PASC agreed that the applicant's revised population 2 was at risk of changing the purpose of the application from the use of cardiac MRI to diagnose myocarditis to the broader use of using cardiac MRI as a triage test before ICA in patients presenting with intermediate-risk ACS – as an alternative to CTCA (as in the population used in the CARMENTA trial).

Intervention

The proposed intervention specified in this Application is cardiac MRI for patients with 1) signs and symptoms suggestive of acute onset cardiomyopathy (acute heart failure and/or arrythmia); 2) ACS that may be due to myocarditis (Applicant, 2022a).

Overview

Cardiac MRI is a non-invasive imaging technique that utilises radiofrequency signals to develop images of the heart and soft tissues (Situ et al., 2020). Cardiac MRI affords the ability to measure, in a single examination, multiple aspects of the structure and function of the heart and vasculature, thus it can assist the diagnosis of myocarditis (Ismail et al., 2022). Cardiac MRI examination include, but are not limited to, assessment of left and right ventricular function, myocardial viability, ischaemia assessment, scar assessment, tissue characterisation, imaging of aorta and great vessels, paediatric and adult congenital abnormality imaging, and imaging of the proximal coronary arteries (Assomull et al., 2007, Rajiah et al., 2013, Romfh et al., 2012, Constantine et al., 2004).

Heart images with high temporal and spatial resolution produced by cardiac MRI are unmatched by echocardiography, especially for precise visualisation of left ventricular anatomy (Russo et al., 2020). Further, its unique ability to non-invasively diagnose cardiomyopathy of tissue characterisation has become a major benefit of cardiac MRI, since the results can exclusively be obtained by invasive EMB.

Worldwide, cardiac MRI has been routinely adopted in clinical practice in Europe (Bruder et al., 2013), the UK and the USA. According to the 2006 international guidelines from the American College of Cardiology (ACC) and the AHA, at least 17 indications appropriate for cardiac MRI have been recognised, including the evaluation of suspected myocarditis (Hendel et al., 2006). Moreover, many international cardiac societies

have already recommend cardiac MRI as the first-line investigation and/or gold standard for a non-invasive approach in the diagnosis of acute myocarditis (Leiner et al., 2020).

Mechanisms

MRI uses high-strength and uniform magnetic fields to scan the human body to produce images for investigating the anatomy, perfusion, function and tissue characterisation of different organs and systems (Grover et al., 2015, Moser et al., 2008). The hydrogen protons in human cells axes line up while exposed to this strong magnetic field, creating a magnetic vector. While small magnetic waves are presented to the targeted area in different frequencies, resonance will be generated. After switching off the radiofrequency source, the magnetic vector will return to its initial state and radiofrequency signals will be released. These signals then convert into a visualisation of the hydrogen proton concentration in the tissue, thus generating an image (Berger, 2002, Hundley et al., 2010).

Development of various cardiac MRI imaging techniques, including late gadolinium enhancement, T1 mapping and T2 mapping, allows visualisation of the myocardium and differentiation between cardiovascular disease of varying aetiology (Demirkiran et al., 2019, Salerno and Kramer, 2009).

Procedure

Cardiac MRI is performed on either a 1.5 T or 3.0 T clinical MRI system (Levine et al., 2007). Most commercially available MRI systems have the capacity to perform cardiac MRI, although specific cardiac sequence licences and a cardiac coil are usually required. For most cardiac MRI examinations, a gadolinium-based contrast agent (GBCA) is administered. An item for the administration of this agent is currently listed on the MBS (item number 63491) (Department of Health, 2004).

During the procedure, the patient is asked to lie within the scanner in a prone or supine position with as little movement as possible. Images are taken during breath holds (approximately 10 seconds) since any movement during imaging can blur the image. A cardiac gating technique is used to synchronise the rhythm of the heart to reduce cardiac artefacts (Saremi et al., 2008). The entire procedure takes 45–60 minutes, depending on local expertise and the complexity of the service.

Notably, cardiac MRI uses neither ionising radiation (or iodinated contrast agents) nor nephrotoxic contrast media (Ersoy et al., 2008). The use of GBCA in cardiac MRI has been widely reported to have favourable side effects compared to the iodinated contrast media used in X-rays and CT imaging (Uhlig et al., 2020). In Australia, GBCAs are available contrast media used in practice for cardiac MRI (MBS item 63491) (Applicant, 2022b).

Cardiac MRI in Australia

The Applicant advises that there are currently 144 accredited cardiac MRI providers (84 cardiologists, 60 radiologists) across every state and in many larger regional centres (Applicant, 2022a). However, access to cardiac MRI for patients with clinically suspected myocarditis remains restricted due to a lack of Medicare funding and rebate (this includes myocarditis due to causes other than mRNA vaccines). MSAC has temporarily approved reimbursement for cardiac MRI only in patients with suspected myocarditis associated with mRNA COVID-19 vaccination (MBS item 63399), pending MSAC consideration of the service following a full health technology assessment process (Department of Health, 2022).

As per the Applicant, the most recent cross-sectional survey of cardiac MRI service conducted by the Royal Australian and New Zealand College of Radiologists (RANZCR) in conjunction with CSANZ found that approximately 15,000 cardiac MRI scans were performed in the 2017 calendar year (Applicant, 2022a). The Applicant claims that a doubling in the number of cardiac MRI scans per year has been observed due to the introduction of new cardiac MRI item numbers and the growing availability of the service nationwide

(Applicant, 2022a). In 2018, MBS item 63395 (cardiac MRI for the diagnosis of ARVC) and 63397 (MRI scan of cardiovascular system for first degree relatives of ARVC patients) were added, while the temporary item 63399 was added in January 2022 (Department of Health, 2022, Department of Health, 2018c, Department of Health, 2018a).

The Applicant anticipates that the advent of new cardiac MRI item numbers for the diagnosis of myocarditis will result in a significant expansion in the number of cardiac MRI services provided and will improve equity of access (Applicant, 2022a).

Diagnosis of myocarditis

The ability of cardiac MRI to provide insight into cardiac tissue characterisation offers unique information to assist in the diagnosis of acute myocarditis. There are several techniques for cardiac MRI (e.g. T1 and T2 mapping, late gadolinium enhancement imaging) which can be used in combination within a single examination (Shehata et al., 2008). Growing evidence suggests that T2 mapping may be a better indicator of acute inflammation than T1 mapping (Ferreira et al., 2018). Several studies suggest that T2 mapping may become an indispensable tool to facilitate non-invasive assessment of inflammation within the myocardium, which is consistent with the Application (Lota et al., 2017).

The updated Lake Louise criteria is used in the cardiac MRI-based diagnosis of myocarditis and is based on at least T1-based criterion and at least one T2-based criterion (Luetkens et al., 2019). The T1 based criterion is considered positive if increase of native T1 relaxation times, increase of extracellular volume (ECV), or positive late gadolinium enhancement (LGE) is present. T2 based criterion is deemed to be positive if T2 relaxation times or in cases with regional high T2 signal intensities on T2-weighted images or increased global T2 signal intensity ratio exists (Gutberlet and Lücke, 2019, Luetkens et al., 2019). Potential risk to the patients

Being a non-invasive test without any associated radiation and limited nephrotoxicity, cardiac MRI has a good safety profile (Nazarian et al., 2017, Naehle et al., 2011, Sokolska et al., 2019).

Prior to the procedure, patients are screened for potential complications, including the presence of non-MRI-compatible implants or cardiac devices (e.g. pacemakers and defibrillators). According to the Applicant, only a few patients (<1%) have non-MRI-compatible implanted cardiac devices unsafe for MRI scanning. We found little published literature on the safety of MRI-compatible (also known as MRI-conditional) implanted cardiac devices. A study by Nazarian et al evaluated the safety of cardiac MRI using a prespecified safety protocol for patients with a legacy pacemaker or legacy implantable cardioverter–defibrillator system. Results showed the absence of long-term clinically significant adverse events (Nazarian et al., 2017, Padmanabhan et al., 2018). In Australia, safety related assessment of implants or devices is available via http://www.mrisafety.com/TMDL_list.php.

In addition, GBCA feasibility should be considered in early and late gadolinium enhancement. Rare acute allergy-like reactions can occur in approximately 0.07% of patients. GBCA administration can put patients with impaired kidney function or end stage kidney disease (referred to as group II in the American College of Radiology classification) at risk of developing fatal nephrogenic systemic fibrosis (Weinreb et al., 2021, Chrysochou et al., 2010, Al-Chalabi et al., 2019).

Finally, according to a study by Melendez et al, a small proportion (n = 31/1160, 2.7%) of patients who have claustrophobia may have difficulty undergoing cardiac MRI, given the narrow diameter of the scanner and the long examination time (Meléndez and McCrank, 1993). For the vast majority of patients with claustrophobia a small amount of light sedation can help overcome their poor tolerance (Applicant, 2022a).

Accreditation and Medicare eligibility requirements

Currently in Australia, the majority of cardiac MRI examinations are performed in an outpatient setting, either in public hospitals, private hospitals or outpatient clinics (Storey P, 2014). The scan is carried out by MRI-trained radiographers, usually under the direct supervision of a cardiac MRI-accredited cardiologist or radiologist. Reporting is carried out by accredited cardiologists and radiologists and imaging trainees. In most large cardiac MRI services, imaging fellows (specialist physician trained in cardiac imaging) can assist with the examination when needed.

To be eligible to claim the existing MBS rebate (item 63395 for the diagnosis of ARVC), a cardiac MRI scan must be performed by an accredited cardiac MRI provider on an MRI system with a Medicare eligibility (either full or partial). The Applicant proposes a similar framework for cardiac MRI as an investigation for myocarditis (Applicant, 2022a).

CSANZ and RANZCR continue to develop the training requirements for specialists supervising and reporting cardiac MRI. Cardiac MRI certification is carried out by a conjoint committee from CSANZ and RANZCR (Diep, 2020).

PASC noted the applicant's advice that the proposed cardiac MRI service is a complex test and should be limited to only those radiologists and cardiologists who have been certified by the Conjoint Committee for Certification in Cardiac MRI (the Conjoint Committee).

Comparator(s)

The Applicant proposes different comparators for cardiac MRI for the two populations with different sets of clinical circumstances.

In population 1, the comparator for signs and symptoms of patients with cardiomyopathy is standard management for clinically suspected acute myocarditis with or without EMB when clinically indicated. In Australian clinical practice, in the absence of cardiac MRI a diagnosis of myocarditis is most commonly established via EMB for the acute cardiomyopathy pathway.

In population 2, for patients with signs and symptoms of ACS, the comparator is standard management for clinically suspected acute myocarditis with/without EMB when clinically indicated after exclusion of obstructive CAD/ ischaemia

Backgrounds and technical descriptions of these procedures are provided below.

Population 1: patients with signs and symptoms of acute onset cardiomyopathy

Overview of EMB

EMB via cardiac catheterisation is currently reimbursed by MBS item 38275. Subsequent histological evaluation provides key diagnostic information, such as characteristics of inflammatory cells, presence of viruses and myocardial fibrosis (Aretz et al., 1987, Sinagra et al., 2021, Caforio et al., 2013a). Immunohistochemical criteria (>14 leucocytes/mm2 including up to 4 monocytes/mm^2 with the presence of CD3 positive T-lymphocytes >7 cells/mm2) are also included to inform a definitive diagnosis of myocarditis (Hazebroek,2014). However, the Applicant suggests that up to 50% of patients who currently undergo a EMB, have a subsequent cardiac MRI to provide a definitive diagnosis because the histology results are non-specific (probably due to the size and amount of tissue obtained and the patchy nature of inflammation) (Applicant, 2022a). In patients with vaccine associated myocarditis, cardiac MRI is the only imaging technique that can conclusively diagnose myocarditis in the absence of left ventricular dysfunction. Left ventricular dysfunction is a late sign of vaccine-associated myocarditis, according to the current definitions used by the Australian Technical Advisory Group on Immunisation for the diagnosis of mRNA vaccine-

associated myocarditis (as per the Brighton Collaboration Case Definition) (Applicant, 2022a, Sexson Tejtel et al., 2022).

In other cases, with a specific suspected aetiology of myocarditis, such as giant cell myocarditis, cardiac MRI is less informative because it does not determine the aetiology of inflammation (Tschöpe et al., 2019). In these patients, initial cardiac MRI usually indicates acute myocarditis, but the patient is severely unwell for unknown reasons, which calls for further investigations (Sujino et al., 2014). Thus, a subsequent EMB and relevant tests are required to provide aetiology evidence and guide a more aggressive immunosuppressive regimen (Tschöpe et al., 2019).

EMB is performed under the guidance of a conjoint scientific statement from the AHA, the ACC and the ESC (Cooper et al., 2007). Based on this statement, the recommended indications for EMB are limited to patients presenting with heart failure. However, clinical applications of EMB for these patients remains controversial. Experts from the *2013 ACC/AHA guideline for the management of heart failure* argued that EMB should be excluded from the routine evaluation of those patients because of limited diagnostic yield and potential complications (Yancy et al., 2013).

PASC noted that there is limited access to EMB in Australia, is technically challenging to perform and may have significant turnaround time for pathology reporting in low-throughput centres (in contrast to accredited cardiac MRI which is potentially more readily available). PASC noted the applicant's advice that EMB is associated with significant patient risk and outcomes are better at high performance centres.

Operative procedure

EMB is often performed in an outpatient setting. A 1–2-mm endocardium and/or myocardium sample is extracted through a biopsy catheter into peripheral vessels. During the procedure, an X-ray or echocardiogram can be performed to direct the EMB catheter to specific sites. Real-time 3-dimensional echocardiography in conjunction with these imaging techniques can improve the accuracy of EMB procedures (Amitai et al., 2007, Platts et al., 2010).

Disadvantages

As an invasive procedure, EMB presents risks for some patients. It has been reported that the complication rate of EMB is approximately 0–6%, including severe and minor complications (Table 5) (Cooper et al., 2007, Bennett et al., 2013, Seferović et al., 2021). The occurrence of complications is closely related to patient characteristics, EMB site, operation volume and professional skills of the operator (Cooper et al., 2007).

Table 5 Severe and minor complications of EMB

Severe complications	Minor complications
Death	Chest pain
Cardiac perforation/haemopericardium/tamponade	Deep vein thrombosis
Pneumothorax/air embolism	Puncture site haematoma/nerve palsy
Thromboembolism	Hypotension/vasovagal syncope
Valvular trauma	Arterial trauma/vascular damage/fistulae
Severe arrhythmias/atrioventricular block	

Abbreviation: EMB = endomyocardial biopsy
Source: (Seferović et al., 2021)

Other limitations, including sampling error and low sensitivity due to uneven distribution of cardiomyopathy, should be considered in the assessment of diagnostic certainty and accuracy (Leone et al., 2012, Zanatta et al., 2019). Cooperation with echocardiography, cardiac MRI and cardiovascular pathology can assist in reducing cardiac misdiagnosis.

Relationship with the proposed diagnostic modality

The Applicant proposes that EMB will be replaced by cardiac MRI as the alternative diagnostic modality for myocarditis among patients with signs and symptoms of cardiomyopathy. However, cardiac MRI cannot completely replace EMB in making definitive diagnosis of myocarditis.

The pathway of accessing cardiac MRI as the alternative diagnostic modality is different to that of the comparator (EMB). At the initial stage, patients are examined by their GP then referred to a specialist for the next level of care. For EMB, patients will be referred to a cardiologist for consultation, followed by a hospital appointment at which the biopsy surgery is performed as a day procedure. In comparison, hospital care for the cardiac MRI pathway is not required. Cardiac MRI is referred by a cardiologist and the imaging is done by an accredited community imaging service.

As an invasive procedure, the decision to recommend EMB is not taken lightly. Among the cohort with signs and symptoms of acute onset cardiomyopathy with suspected myocarditis (population 1), only patients with new onset of heart failure or with unknown cause of cardiomyopathy will undergo the biopsy procedure. Thus, EMB will only be performed under clear indications to inform therapeutic management. This is a subset of the proposed population in real-world clinical setting. In comparison, indications for cardiac MRI can be much wider because cardiac MRI is also considered the gold standard for myocarditis diagnosis for non-EMB indicated patients (Cundari et al., 2021). Therefore, it is clear that cardiac MRI is not merely an EMB replacement but offers this imaging modality to a wider group of patients.

For a small group of patients, EMB could not be replaced by cardiac MRI due to specific reasons. For example, severely unwell patients with end stage heart failure indicated for heart transplantation would require a biopsy procedure for tissue typing despite the fact that cardiac MRI could offer clear and definitive diagnostic information. Moreover, at times cardiac MRI may not be feasible due to haemodynamic instability. In these cases, cardiac MRI may be unnecessary.

Standard management

Currently there is no cure for myocarditis, but management relates to the aetiology. Treatment of myocarditis includes standard management to patients with various types of myocarditis or cardiomyopathy as well as therapy targeting specific disorders. Cause-specific or nonstandard treatment of myocarditis depends on further molecular diagnosis, clinical presentation and histology. Standard management includes various nonspecific guideline-directed measures, e.g. heart failure therapy, mechanical circulation aid, treatment/control of arrythmias, and in specific patients, anticoagulation (Camm et al., 2012, Yancy et al., 2013, Caforio et al., 2013b, Bozkurt et al., 2016b).

For population 1, PASC noted that the comparator for patients who might not be indicated for or are contraindicated for EMB (e.g. unstable haemodynamics, valvular disease or coagulopathy) would be standard management. Therefore, the comparator for population 1 should be: standard management for clinically suspected acute myocarditis with/without EMB when clinically indicated. The clinical context of the standard management for population 1 has also been provided in the main body of the PICO comparator section. These changes are also reflected in the clinical algorithms.

Population 2: patients with signs and symptoms of ACS

In this population, patients present clinically with signs and symptoms of ACS. ACS is a manifestation of CAD, and it is usually the result of a disrupted coronary artery plaque (known as atherosclerosis). Common symptoms include anginal chest pain, heart attack (myocardial infarction), elevated cardiac biomarkers, or other complications such as heart failure-type syndrome (Mosebach et al., 2019). Conditions that present with signs and symptoms of ACS are presented in Table 6.

Table 6 Common conditions that present with signs and symptoms of ACS

Cardiopulmonary pathology	Aortic dissection Cardiac tamponade Takasubo or Hypertrophic cardiomyopathy Myocarditis Pericarditis Pneumothorax Pulmonary embolism
Gastrointestinal disease	Biliary colic, cholecystitis and cholangitis Esophageal rupture Pancreatitis Peptic ulcer and gastritis
Musculoskeletal	Chest wall pain (costochondritis)
Others	Anemia Anxiety Panic disorder

Source: (Husainy et al., 2013, Herath et al., 2016, Liu et al., 2009)

As recommended by ESC, an invasive ICA (MBS item 38244) or non-invasive cardiac CT (MBS item 57360) should be performed in patients with an ACS-like presentation, as well as in other clinical scenarios where it is necessary to rule out eventual underlying CAD (Caforio et al., 2013a, Adler et al., 2015). In population 2, both ICA and cardiac CT are appropriate comparators.

The differential diagnosis of ACS includes apparently non-significant coronary disease (e.g. unstable plaque event, embolus, spasm, flush ostial occlusion of a branch artery), takotsubo cardiomyopathy, pericarditis, and myocarditis (Jeremias and Gibson, 2005). Young patients with a classic history consistent with acute myocarditis and no cardiovascular risk factors may not need a ICA if immediate access to cardiac MRI is available (Polte et al., 2022).

ICA

Overview

ICA is considered as the gold standard test for identifying the presence and extent of atherosclerotic CAD. It is also used for identifying valvular and other structural abnormalities and for measuring hemodynamic parameters (Tavakol et al., 2012). In this application, where there is some overlap between ACS/CAD and myocarditis, selective ICA is often used as the first-line procedure to exclude the possibility of CAD (Caforio et al., 2013a).

Subsequent coronary intervention is performed in only about 40% of patients undergoing ICA (Gorenoi et al., 2012). Moreover, it has been reported that up to two-thirds of patients undergoing ICA present with unobstructive coronary arteries (Patel et al., 2010). Considering the low pre-test probability for CAD and the significant radiation exposure of ICA, cardiac CT can be performed where available as an alternative to exclude CAD in real-world settings (Tarighatnia et al., 2017, Mirna et al., 2022). Thus, ICA and potential complications (described below) can be avoided in a large number of patients.

Operative procedure

ICA involves light sedation and local anaesthetic of either the femoral, brachial or radial area. Young children will require a general anaesthetic.

Catheters are inserted via an arterial puncture to inject contrast selectively into the coronary arteries, along with an injection of contrast into the left ventricle to assess left ventricular function, and measurement of haemodynamic pressures (Leipsic et al., 2014, Hamid, 2014). A series of X-ray images are taken to assess

narrowing or blockages in the coronary arteries. The procedure usually takes 0.5–2 hours and outpatients are able to go home the same day.

Of note, treatments such as angioplasty or stenting, can sometimes be done during the ICA procedure (Fischman et al., 1994, Serruys et al., 1994).

Complications

There are no absolute contraindications to having ICA; however, risks can be associated with cardiac and non-cardiac complications. The general medical profile of the patient such as age, renal insufficiency, diabetes mellitus, morbid obesity and underlying cardiovascular status can increase the risk of complications. Major complications attributed to cardiac catheterisation occur in less than 2% of the population, with mortality of less than 0.08% (Tavakol et al., 2012). The risks and complications associated with ICA are presented in

Table 7.

Table 7 Risks and complications of ICA

Allergic and adverse reactions • Allergy to local anaesthesia • Allergy to general anaesthesia • Adverse reaction to contrast media • Heparin induced thrombocytopenia
Infection
Nephropathy • Contrast induced nephropathy
Cholesterol emboli
Local vascular injury • Hematoma and retroperitoneal haemorrhage • Pseudoaneurysm • Arteriovenous fistula • Dissection of the femoral and iliac arteries • Thrombosis and embolism
Conduction disturbances • Bradyarrhythmia • Tachyarrhythmia
Death
Myocardial infarction
Cerebrovascular complications
Dissection and perforation of great vessels
Other complications • Hypotension • Hypoglycaemia • Respiratory insufficiency

Source: (Tavakol et al., 2012)

Cardiac CT of the coronary arteries (CTCA)

Overview

There have been technological advances in the use of cardiac CT as a diagnostic tool for CAD over the past decades (Weininger et al., 2011). CAD is considered as the major underlying cause of ACS. The cardiac CT scan, which is a non-invasive method also referred to as cardiac CT angiography or coronary CT angiography or CTCA, can accurately determine the presence and extent of CAD and improve the early and accurate prioritisation of patients with chest pain (Seneviratne et al., 2007). In this application, cardiac CT is an appropriate comparator since it has become a viable and effective alternative to ICA in the diagnosis of myocarditis and excluding CAD and/or ACS.

Cardiac CT is a non-invasive test used to identify the presence of coronary obstruction and has been shown to have an excellent negative predictive value of 83% (95% CI, 75 to 89) (Nazir and Nicol, 2019, Miller et al., 2008). According to the 2013 ESC guidelines on the management of stable CAD, cardiac CT is recommended for lower-risk chest pain patients, while the 2016 NICE guideline recommends the use of cardiac CT for investigating anginal chest pain in patients with suspected coronary disease (Moss et al., 2017).

Under MBS item 57360, cardiac CT is performed on a minimum of a 64-slice (or equivalent) scanner, where a request is made by a specialist or consultant physician, the patient has stable symptoms consistent with coronary ischemia, and the patient has a low to intermediate risk of an acute coronary event with no significant cardiac biomarker elevation and no ECG changes indicating acute ischemia (Department of Health, 2018b).

Radiological procedure

Premedication such as the use of beta blockers is usually given prior to cardiac CT to reduce the heart rate (Pannu et al., 2006). After completing questions on allergies, medical history and medications, intravenous access will be obtained, and ECG electrodes will be connected to allow ECG-gated image acquisition. For optimum image acquisition, further intravenous beta blockers may be administered to reduce heart rate to about 60 bpm (Hoffmann et al., 2006) The patient's blood pressure should be monitored and no medication should be given if the patient's systolic blood pressure is <100 mm Hg (Wallis et al., 2012).

For diagnostic cardiac CT, approximately 70–100 ml of contrast is required to achieve the best possible opacification of the coronary arteries. The patient's circulation can be tested by administration of a 20-ml test bolus of contrast to track the density of the contrast in the ascending aorta, or via the bolus-tracking technique whereby the main injection is provided and the scan is prompted when adequate contrast is seen in the ascending aorta (Wallis et al., 2012).

The generation of images in the scanning acquisition phase involves ECG gating, which enables collection of data from the same point in the cardiac cycle over consecutive heart beats (Pannu et al., 2006). Scanners with higher detector rows or slices are able to obtain more images of the cardiac volume in one rotation. The number of CT slices produced per rotation is comparable to increasing the number of lenses in a film camera. The larger the number of slices, the larger the volume of the heart captured by rotation. An image or collage of the whole heart can be created using multiple pictures of the heart with lower slice numbers (16–64 slices). Scanning with a higher number of slices allows the capture of the whole heart volume in a single rotation and has a higher temporal resolution, producing a higher-quality diagnostic image of the heart and its blood supply (Hoffmann et al., 2006).

Complications

The risks associated with cardiac CT are as follows:

Radiation exposure

The high degree of ionising radiation that may be involved in cardiac CT can harm living tissue and lead to a higher risk of cancer (Lee et al., 2017, Huang et al., 2010). The level of exposure to patients depends on the type of machine used. Table 8shows the lifetime risks of cancer from a single 64-slice CT coronary angiogram, according to the study by Einstein et al (Einstein et al., 2007).

Table 8 Estimated lifetime risk of cancer from a single 64-slice CT coronary angiogram

	Lifetime risk of cancer	
Age (years)	Male	Female
20	1 in 686	1 in 143
40	1 in 1,007	1 in 284
60	1 in 1,241	1 in 466
80	1 in 3,261	1 in 1,338

Effects on cardiac devices

Cardiac CT is a robust non-invasive imaging modality that can yield an accurate diagnosis and exclude CAD with high diagnostic accuracy (Tatsugami et al., 2016). However, accurate assessment of the coronary arteries is limited by metal artefacts produced by pacemakers or implanted cardioverter defibrillator leads (Tatsugami et al., 2016, DiFilippo and Brunken, 2005, Sosnowski et al., 2010). Complications in the use of cardiac CT for patients with cardiac devices include lead perforations and the rare likelihood of CT interference (Mak and Truong, 2012).

Allergic reactions

Iodine is the main component of all intravenous contrast agents for CT, including the non-ionic dyes (Biyase, 2020). Intravenous contrast has the possibility to cause allergic reactions manifesting as transient skin rash, metallic taste, nausea, asthma or severe anaphylaxis. Life-threatening reactions occur in 0.2% of patients, depending on the type of iodinated contrast media used (Bottinor et al., 2013).

Precautions in certain medications

Caution should be exercised in the administration of cardiac CT for patients on certain medications. For example, application of nitrates is recommended in recent guidelines to improve the quality of CT scan by enhancing contrast (Abbara et al., 2016, Takx et al., 2015). Nitrates should be avoided if the patient is taking a phosphodiesterase inhibitor (e.g. sildenafil [Viagra]), which could precipitate pronounced hypotension (Abbara et al., 2016).

Relationship with the proposed diagnostic modality

The Applicant proposes that ICA and cardiac CT will be replaced by cardiac MRI as the alternative diagnostic modality for myocarditis among patients with suspected ACS. This replacement may require clinical context and more detail regarding how eligible patients can be identified.

The pathway of accessing cardiac MRI as the alternative diagnostic modality differs from the comparator (i.e. ICA and cardiac CT). Patients who have very minor symptoms and are not severely unwell can have initial investigations performed in the primary care setting, as long as the results of investigations can be obtained and reviewed by the referring practice within 12 hours (as discussed above, *Route for accessing care*). Otherwise, patients in this pathway typically present to the ED with acute chest pain, with subsequent admission to a day-stay or short-stay ward. Thus the invasive ICA is usually performed as an inpatient or as an expedited outpatient investigation in a hospital radiology department. Patients may be referred by their GP to a cardiologist for a coronary angiogram. Cardiac CT and cardiac MRI are referral services from a cardiologist where the scanning is done at an accredited community imaging service. For patients who have normal investigative results but persistent symptoms, investigations should be repeated in the community and in the worst cases, ED referral is required.

Cardiac MRI as the proposed imaging modality is used to diagnose myocarditis in the current PICO Confirmation. The comparator imaging technologies (ICA and cardiac CT) are primarily used for diagnosing CAD. Therefore, they are different in their purposes and likely to target different patient groups. Patients with ACS signs and symptoms can have a wide spectrum of clinical presentations, as a result of the differential diagnoses. For a better understanding of the relationship between the intervention and the comparator, patients with ACS signs and symptoms can be separated into two groups: 1) those with suspected significant CAD (i.e. high risk of CAD based on risk stratifications), and 2) those indicated for low to intermediate severity of CAD. The CAD risk stratification tests include, but not limited to, lipid profile, diabetes risk assessment, blood pressure, and body mass index.

For the first group of patients—those with a high risk of having CAD—cardiac MRI may have limited value for diagnosing myocarditis. For these patients, the significant probability of CAD is likely to be ascertained through conventional and routine diagnostic pathways (e.g. TTE, MPS and stress tests). Instead of cardiac MRI, timely ICA procedures are most likely to be used. Patients in the most severe spectrum of CAD are likely to present to an ED with a limited timespan for life-saving interventions. For example, patients with STEMI should have primary percutaneous intervention at the earliest stage and for those who cannot, prompt fibrinolytic therapy remains the second line life-saving option (Keeley et al., 2003, Fibrinolytic Therapy Trialists' (FTT) Collaborative Group, 1994). Early transfer for primary percutaneous intervention within 6 hours after fibrinolytic therapy is associated with fewer ischaemic complications (Cantor et al., 2009). Cardiac MRI is not applicable under these circumstances. Further, cardiac MRI has certain capacities to

detect CAD, as noted previously. When cardiac MRI is performed instead of ICA (or cardiac CT) for these patients, it shifts the focus population from myocarditis to clinically suspected CAD. Therefore, these patients should not be within the scope of this Application; cardiac MRI and ICA (or cardiac CT) should not be compared for these patients.

The second group of patients—those with low to intermediate ACS mimic severity spectrum—is more likely to fit the proposed population. For these patients, differential diagnosis using various technologies and techniques (e.g. TTE, MPS and stress tests) may still be required prior to invasive investigations such as ICA. When CAD is suspected but cannot be distinguished from myocarditis, cardiac MRI may have value to avoid invasive investigations and ionising radiations. In current real-world settings in Australia, cardiac MRI has been performed in a small number of cases to exclude CAD and hence avoid invasive ICA. Patients pay for the scan out-of-pocket due to the lack of MBS reimbursement. Under this scenario, cardiac MRI would result in a reduction in the number of patients requiring ICA and cardiac CT. It is important to clarify that ICA and cardiac CT are used as differential diagnoses for myocarditis, whereas cardiac MRI can detect myocarditis in a more direct manner. Therefore, such a comparison may not be direct in terms of quantitative evidence for diagnostic accuracy outcomes.

In population 2, for patients with signs and symptoms of ACS, PASC noted that the comparator should be: standard management for acute myocarditis with/without EMB when clinically indicated after exclusion of obstructive CAD/ ischaemia (with ICA or CTCA or other investigations).

PASC noted that the comparator for population 2 in the current PICO is different from what was proposed in the Application form. The Applicant proposed the ICA or CTCA as the comparator, which PASC considered were not appropriate as they are not diagnostic tests for myocarditis but rather done to exclude (or confirm) obstructive CAD as the likely cause of presentation. Given the patient presentation with generic signs and symptoms, these would be prior tests required to define the agreed patient population- rather than comparators for cardiac MRI. However, PASC noted the applicant's advice that in clinical practice, patients classified with a low pre-test likelihood of CAD would not receive ICA or CTCA to exclude (or confirm) obstructive CAD (as they would receive cardiac MRI before these investigations if available, and if myocarditis was diagnosed following cardiac MRI, they would not need further investigations to rule out obstructive CAD). Due to the clarifications needed around the Population 2 including the need to stratify the population for pre-test likelihood for obstructive CAD, the comparator(s) for this population (and any defined subgroups) may be subject to change.

At its December 2022 meeting, PASC noted the applicant advocated that the comparator investigations in the revised intermediate ACS risk population (population 2) is CTCA to rule out obstructive CAD first and then assessment of cardiac function with TTE - as there is no true comparator test because myocarditis is a diagnosis of exclusion. The applicant advised that avoidance of these comparator investigations would be the most important change in patient management, as it would reduce exposure to CTCA (or ICA) which is associated with risk of reaction to iodinated contrast agents and radiation exposure to patients compared with cardiac MRI which does not present these risks.

PASC accepted that CTCA plus TTE should be included as a comparator in the revised population 2.

Reference standard (for investigative technologies only)

The gold standard test to identify myocarditis remains a controversial issue, with some investigators using EMB and others relying instead on a combination of clinical, laboratory, ECG and angiographic findings (Abdel-Aty et al., 2005). One systematic review and meta-analysis of cardiac MRI for the diagnosis of acute

myocarditis in adult patients, included studies which had used either EMB or clinical criteria for the diagnosis of acute myocarditis as the reference standard (Kotanidis et al., 2018).

The reference standard for the assessment of diagnostic accuracy may be either EMB or clinical criteria (i.e. a combination of clinical, laboratory, ECH and angiographic findings). The diagnostic criteria for myocarditis were discussed in full previously (see *Clinical presentation* and diagnostic criteria in the Population Section).

PASC considered that the reference standard for cardiac MRI is EMB, given it is accepted as the gold standard for the definitive diagnosis of myocarditis.

Outcomes

There is significant overlap regarding the proposed outcome in the two populations as to patient relevant outcomes (safety, performance, patient management, health and non-health outcomes) and healthcare system outcomes. The outcomes listed below will be evaluated for the population with signs and symptoms suggestive of acute or fulminant onset cardiomyopathy and with signs and symptoms of ACS (Table 9).

Table 9 Outcomes

Outcomes	Population 1	Population 2
Patient related outcome		
Safety		
Rates of inappropriate therapy	✓	✓
Adverse events arising from the intervention and comparator procedures		
Contrast adverse reaction	✓	✓
Exposure to ionising radiation		✓
Claustrophobia requiring the administration of sedation or general anaesthetic	✓	✓
Performance outcomes		
Sensitivity and specificity	✓	✓
Positive likelihood ratio, negative likelihood ratio	✓	✓
ROC curves	✓	✓
Number of non-diagnostic tests	✓	✓
Diagnostic yield	✓	✓
Patient management outcomes		
Diagnostic utility	✓	✓
Change in clinical diagnosis	✓	✓
Prognostic utility	✓	✓
Predictive utility - change in treatment pathway, including:		
Commencement of appropriate targeted or non-targeted treatment	✓	✓
Need for subsequent EMB	✓	✓
Health outcomes		
Cardiovascular-related morbidity (including chronic heart failure therapy, hospitalisations for heart failure, need for CRT/ICD/device-related therapy), cardiac transplantation.	✓	✓
Cardiovascular-related mortality	✓	✓
All-cause mortality	✓	✓
Health-related quality of life	✓	✓
Non-health outcomes*		
The value of knowing, including:		

Outcomes	Population 1	Population 2
Impact on patient behaviour (avoid / resume exercise)	✓	✓
Healthcare system		
Costs associated with the intervention and comparator procedures including costs of appointments, gadolinium-based contrast administration, blood test	✓	✓
Costs associated with adverse events for the intervention and comparator	✓	✓
Incremental cost-effectiveness ratio	✓	✓
Total Australian Government healthcare costs	✓	✓

** PASC considered that prognostic utility could also be categorised as a non-health outcome (e.g. value in knowing).*

Acute myocarditis usually presents as a self-limiting condition with cardiac symptoms resolving once the myocarditis cause such as infection subsides. Because of this, the treatment choices are not likely to be affected by the MRI result. Outcomes that indirectly influence patient management (non-health benefit and harm) as well as the economic efficiency of the health system can be included assessing the value of diagnostic information to healthcare (Wurcel et al., 2019).

The value of knowing was included as a non-health patient-relevant outcome due to the minimal impact of the intervention on treatment. The information provided by the diagnostics may indirectly influence patient management, and even economic efficiency of the health system, rather than directly impact therapeutic decision-making, for which clinical effectiveness and safety can be clearly demonstrated. Possible benefits attributable to the value of knowing include patient empowerment from the value of knowing and deciding, reassurance or the sense of self control provided by knowing, increased sense of well-being and satisfaction, possibility of positive behaviour change, possible connection to people with the same condition for peer support and seeking education and social care (Wurcel et al., 2019, Rizzo and Lee, 2014). Family, caregivers, healthcare providers and society may also benefit from the value of knowing.

PASC noted that the majority of outcomes are appropriate. PASC considered that, 'cardiovascular-related morbidity (including chronic heart failure therapy, hospitalisations for heart failure, and need for cardiac resynchronisation therapy (CRT)/ implantable cardioverter defibrillator (ICD/device-related therapy)' should be included as health outcomes, and (for Population 2) 'cessation of inappropriate treatment' (for CAD) should be removed. For non-health outcomes, PASC noted that the main value of knowing for the proposed population is to inform the ability to either resume or avoid exercise.'. PASC noted this determination is currently predicated on the resolution of symptoms, biomarkers, left ventricular dysfunction and ECG changes, including arrhythmias (at rest and exercise), and that the clinical significance of persistent late gadolinium enhancement on CMR in an asymptomatic individual with clinically healed myocarditis is unknown[3]*. PASC advised that the secondary outcomes related to the related to the COVID-19 or COVID-19 vaccinations be removed, because they are not the major claims of this application, and would be encompassed by the application should it be successful.*

At its December 2022 meeting, PASC considered that prognostic utility could also be categorised as a non-health outcome (e.g. value in knowing).

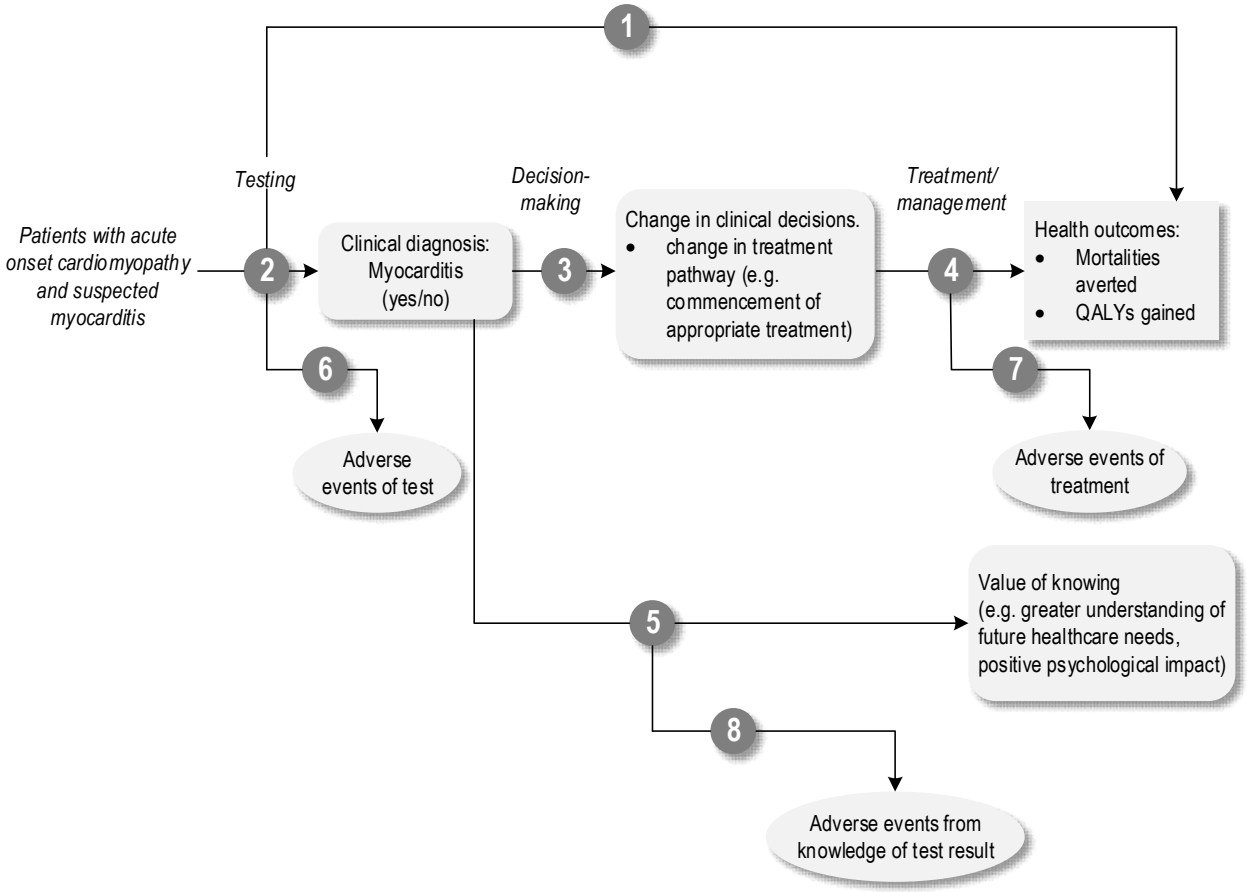
[3] Eur Heart J. 2019 Jan 1;40(1):19-33. doi: 10.1093/eurheartj/ehy730. PMID: 30561613

Assessment framework (for investigative technologies)

Cardiac MRI, an investigative technology, benefits patients by impacting subsequent management decisions. In addition, the act of receiving a diagnosis of myocarditis may add value to the patient journey in other ways (i.e. value of knowing).

Population 1: patients with signs and symptoms of acute onset cardiomyopathy

Figure 1 Assessment framework for population 1: patients with signs and symptoms of acute onset cardiomyopathy



Abbreviations: QALY = quality-adjusted life year

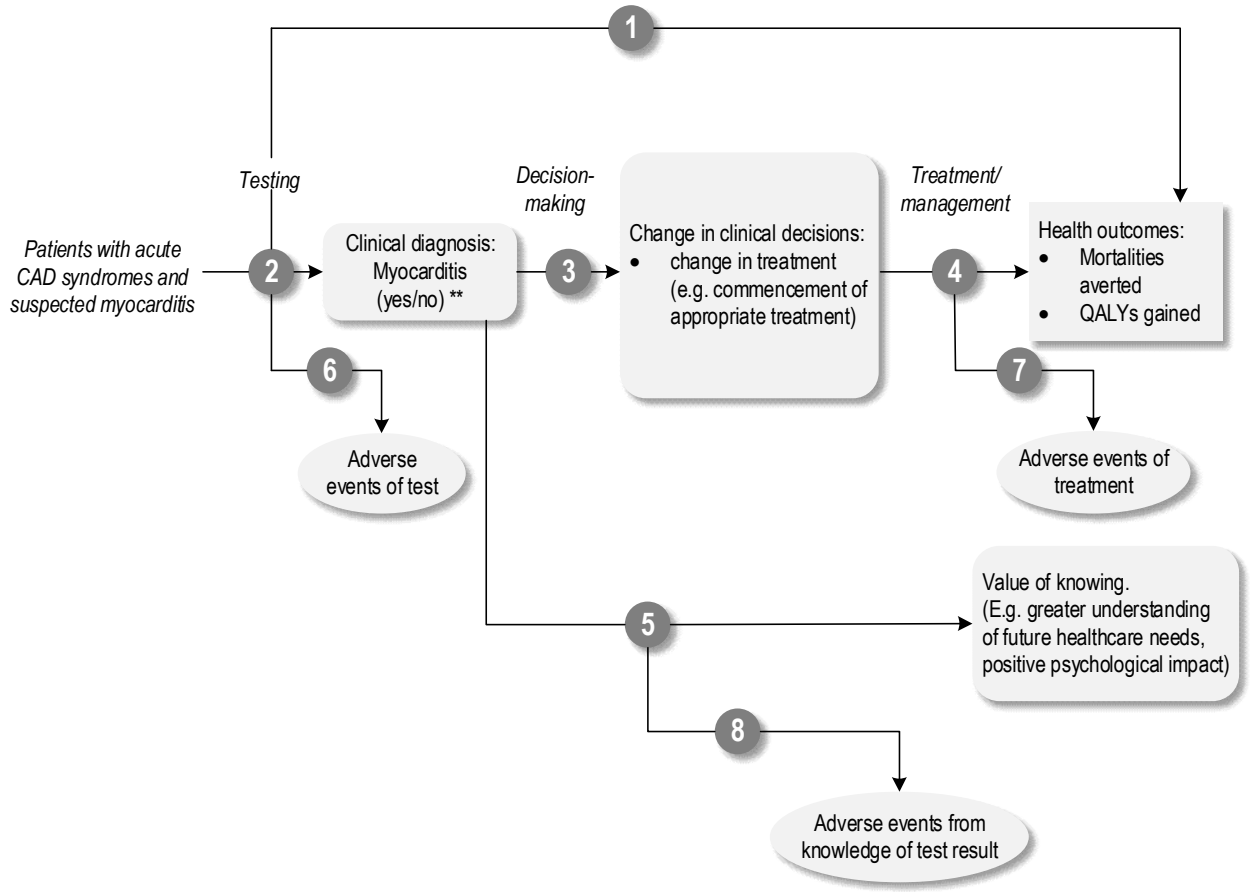
Figure notes:

1: direct from test to health outcomes evidence; 2: test accuracy; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: benefits associated with the value of knowing; 6: adverse events due to testing; 7: adverse events due to treatment; 8: harms associated with the value of knowing

PASC agreed with the assessment framework for population 1.

Population 2: patients with signs and symptoms of ACS

Figure 2 Assessment framework for population 2: patients with signs and symptoms of ACS



Abbreviations: CAD = coronary artery disease; QALY = quality-adjusted life year
Figure notes:
1: direct from test to health outcomes evidence; 2: test accuracy; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: benefits associated with the value of knowing; 6: adverse events due to testing; 7: adverse events due to treatment; 8: harms associated with the value of knowing
** Cardiac MRI (or the comparator) may also provide information to inform a diagnosis of CAD; however, such information is beyond the scope of the current assessment.

PASC noted that, in population 2, the 'avoidance of inappropriate therapies for CAD' should be deleted because if the patient already had obstructive CAD ruled out (with ICA or CTCA or other investigations), they would not have therapies for CAD. As the clinical position of cardiac MRI requires further clarification, the assessment framework for population 2 remains uncertain. Upon the finalisation of the population, the assessment framework will be updated as required.

Clinical management algorithms

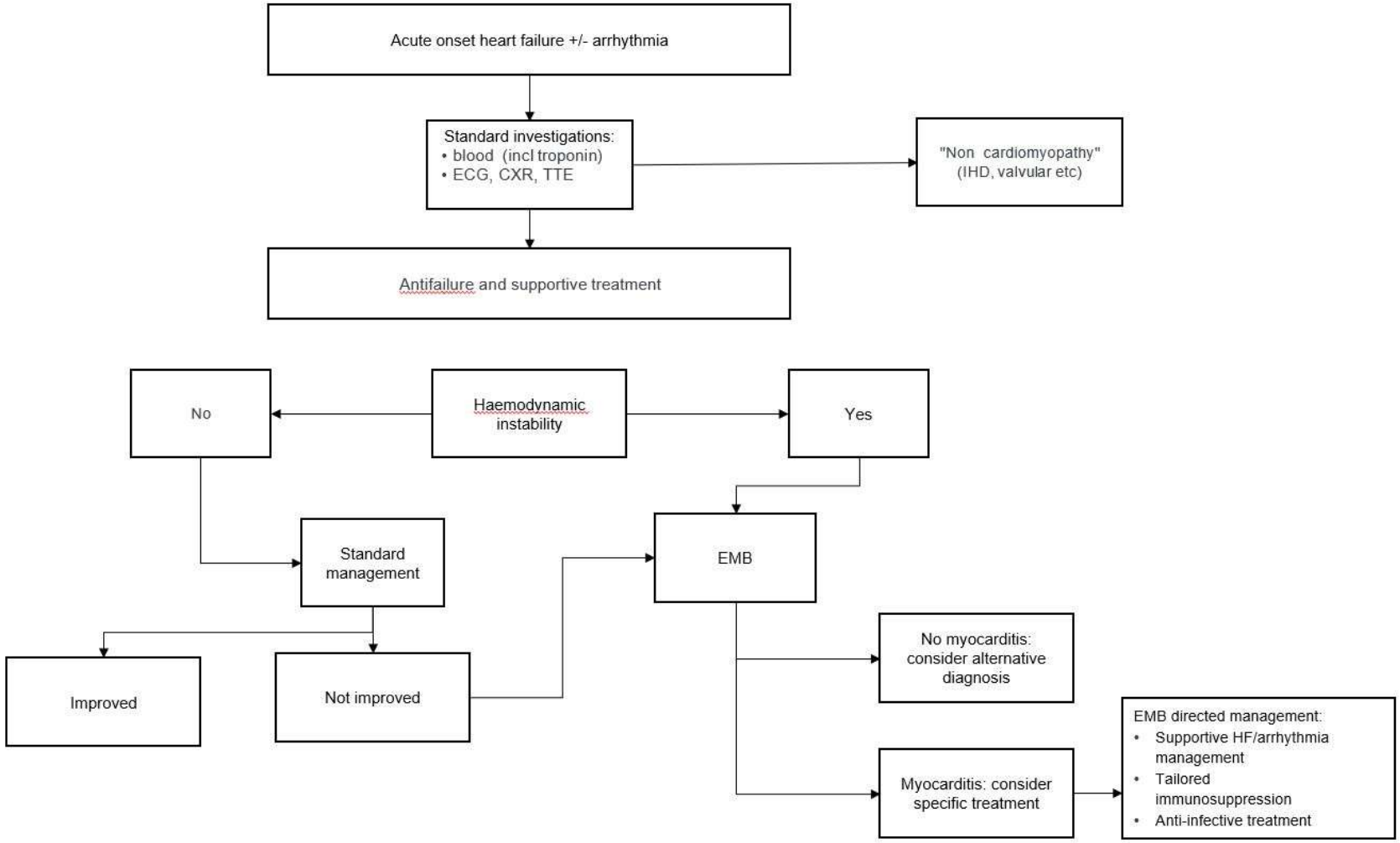
The Applicant provided both the current and the proposed clinical management algorithms for the two proposed populations. The algorithms were reviewed and updated based on the discussion and feedback from the pre-PASC meeting and the Department policy papers. The updated algorithms are presented separately for the two proposed populations. Critical discussion points are provided following the diagrams. The original algorithms provided in the Application form are provided as an appendix at the end of the document.

Based on PASC's discussion, the clinical algorithms for both populations were updated. The new algorithms aimed to highlight any key clinical decision-making points as well as to illustrate clearly where the differences are between the current and the proposed pathways.

Population 1: patients with signs and symptoms of acute onset cardiomyopathy

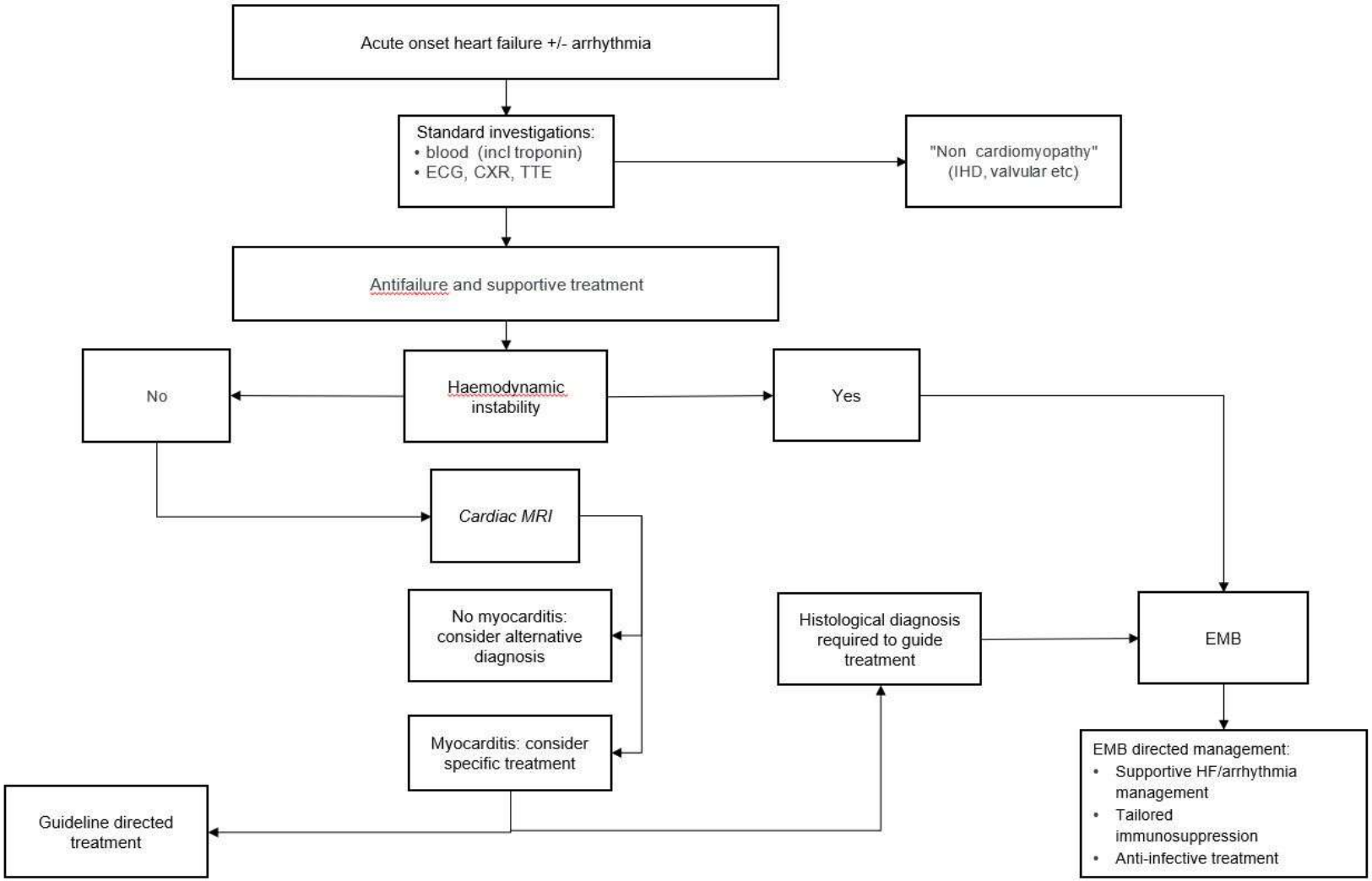
The current (Figure 3) and the proposed (Figure 4) clinical management pathways for myocarditis in patients with acute cardiomyopathy.

Figure 3 Current clinical management algorithm for population 1: patients with signs and symptoms of acute onset cardiomyopathy



Abbreviations: CXR = chest X-ray; ECG = electrocardiogram; EMB = endomyocardial biopsy; HF = heart failure; IHD = ischaemic heart disease; TTE = transthoracic echocardiogram
Source: Updated based on PASC December 2022

Figure 4 Proposed clinical management algorithm for population 1: patients with signs and symptoms of acute onset cardiomyopathy



Abbreviations: CXR = chest X-ray; ECG = electrocardiogram; EMB = endomyocardial biopsy; HF = heart failure; IHD = ischaemic heart disease; TTE = transthoracic echocardiogram
Source: Updated based on PASC December 2022

The current clinical diagnostic pathway starts with patients presenting signs and symptoms of acute onset of heart failure with or without arrythmia. These patients will then undergo the standard investigative tests to investigate their conditions. Standard tests include blood test (including troponin), ECG, chest X-ray and TTE. The haemodynamic stability will then be assessed and managed to guide the myocarditis diagnostic and management pathways (Kociol et al., 2020). Standard management for acute cardiomyopathy will be given to the patient. If the patient's condition does not improve over time, EMB is recommended for definitive diagnosis of myocarditis.

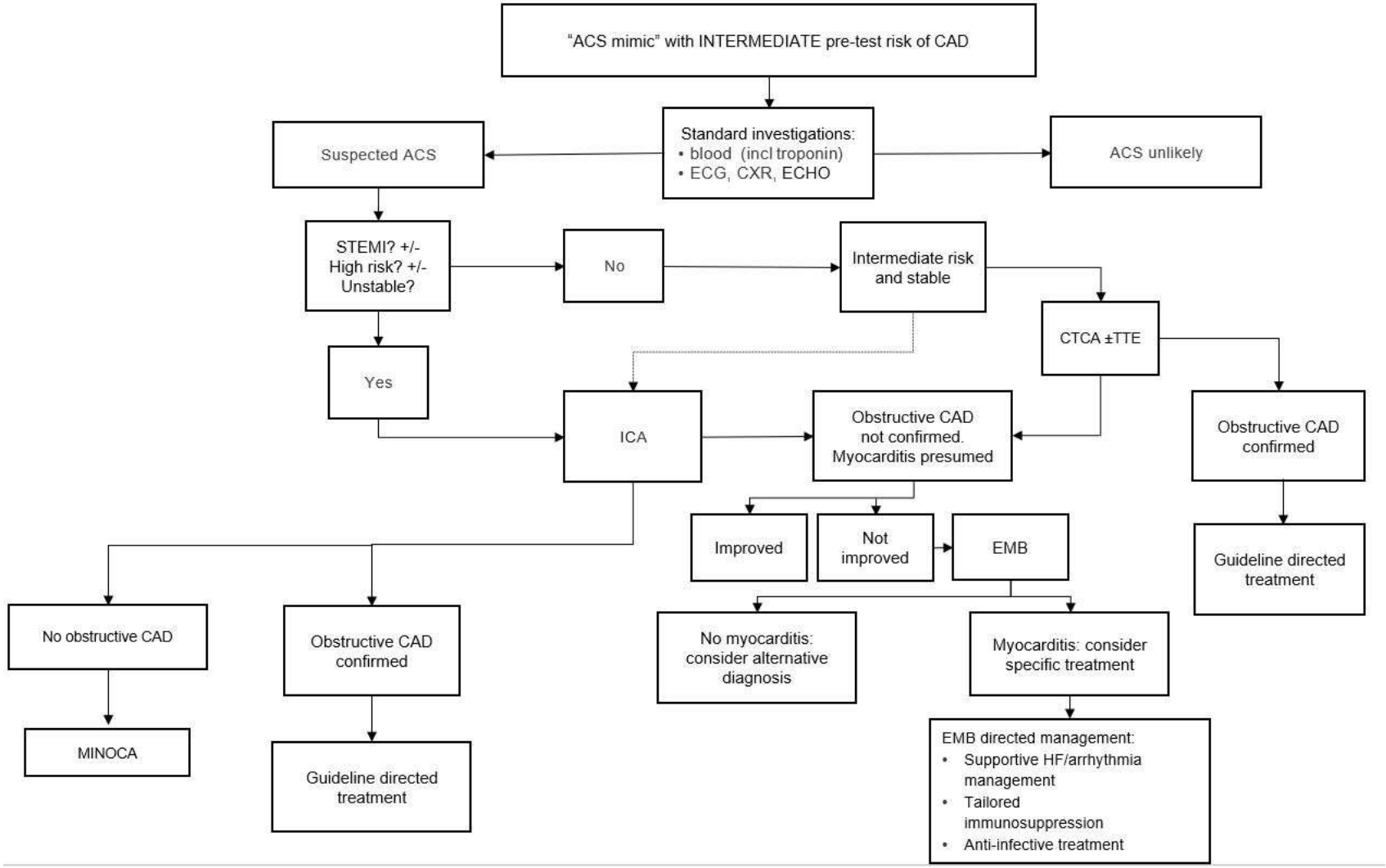
In the proposed clinical management pathway, patients with signs and symptoms of acute cardiomyopathy due to suspected acute or fulminant myocarditis who are hemodynamically stable, cardiac MRI can be used to diagnose clinically suspected myocarditis using the updated Lake Louise criteria. However, EMB is still indicated if a more specific diagnosis is required to guide cause-specific management of myocarditis. EMB is recommended for patients who are hemodynamically unstable for a definitive diagnosis of myocarditis. According to the applicant, it is expected that in the vast majority (approximately 80%) of patients an invasive EMB will not be required if cardiac MRI is performed. In some instances, where the cardiac MRI suggests acute myocarditis but the patient is severely unwell and a specific aetiology of myocarditis (such as giant cell myocarditis) is sought, an invasive biopsy may still be performed to direct a more aggressive immunosuppressive regime (Applicant, 2022a). EMB is also recommended and considered to be the gold standard for monitoring heart transplant rejection (Seferović et al., 2021). For up to 50% of patients who currently undergo invasive EMB the histology is non-specific, and in these instances, cardiac MRI is often performed (when available) to provide diagnostic certainty (Applicant, 2022a). In this Application, non-invasive cardiac MRI rather than EMB, could be performed in this patient group to diagnose myocarditis.

For population 1, PASC noted that for patients with signs and symptoms of acute cardiomyopathy with suspected acute or fulminant myocarditis, evaluation of haemodynamic stability is necessary to aid in deciding the pathway for diagnosing and managing myocarditis. This decision point has been added to the algorithms in both the current and the proposed pathway. In addition, the standard management of acute cardiomyopathy in the current pathway was also added as per the PASC suggestion. Whether or not outcomes of the standard management should be used to determine the eligibility of cardiac MRI may require further clarification.

Population 2: patients with signs and symptoms of ACS

Figure 5 and Figure 6 outline the current and proposed clinical management pathways for detecting myocarditis in patients with ACS mimic.

Figure 5 Current clinical management algorithm for population 2: patients with signs and symptoms of ACS

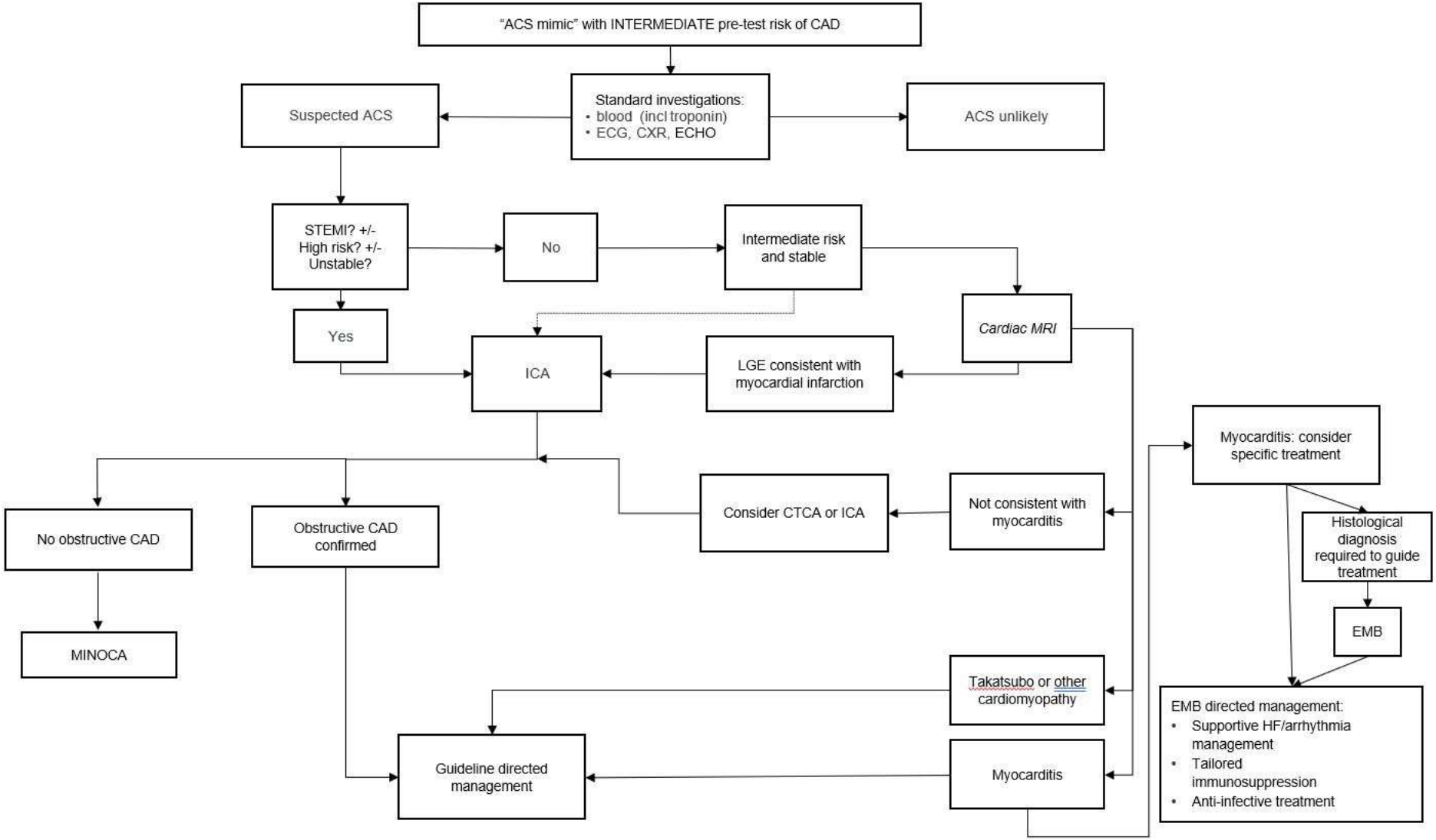


Abbreviations: ACS = acute coronary syndrome; CAD = coronary artery disease; CTCA= CT coronary angiography; CXR = chest X-ray; ECG = electrocardiogram; EMB = endomyocardial biopsy; HF = heart failure; ICA = invasive coronary angiography; IHD = ischaemic heart disease; MINOCA = myocardial infarction with non-obstructive coronary arteries; STEMI = ST elevation myocardial infarction; TTE = transthoracic echocardiogram
Source: Updated based on PASC December 2022

Note, The European Society of Cardiology[4] developed the first international position article on MINOCA and proposed the following MINOCA criteria: (1) AMI criteria as defined by the "Third Universal Definition of Myocardial Infarction"(2) nonobstructive coronary arteries as per angiographic guidelines, with no lesions ≥50% in a major epicardial vessel; and (3) no other clinically overt specific cause that can serve an alternative cause for the acute presentation

[4] Agewall S, et al on behalf of the WG on Cardiovascular Pharmacotherapy. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. Eur Heart J. 2017;38:143–153. doi: 10.1093/eurheartj/ehw149

Figure 6 Proposed clinical management algorithm for population 2: patients with signs and symptoms of ACS



Abbreviations: ACS = acute coronary syndrome; CAD = coronary artery disease; CTCA= CT coronary angiography; CXR = chext X-ray; ECG = electrocardiogram; EMB = endomyocardial biopsy; HF = heart failure; ICA = invasive coronary angiography; LGE = Late gadolinium enhancement; MINOCA = myocardial infarction with non-obstructive coronary arteries; MRI = magnetic resonance imaging STEMI = ST elevation myocardial infarction; TTE = transthoracic echocardiogram; ECHO = transabdominal echocardiogram

Source: Updated based on PASC December 2022

In the current clinical management pathway for diagnosing myocarditis in "ACS mimic" patients with signs and symptoms of ACS, patients with suspected CAD were given either an EMB or cardiac CT to confirm not only the diagnosis of myocarditis but also that of ACS. The stress test and TTE inform clinicians on a patient's level of risk for CAD (McLellan A, 2012). However, it is understood that not all patients will receive TTE and stress tests, and the utilisation of these tests depends on the patient's individual circumstances and how unwell the patient is. The timing of testing is important in myocarditis detection. According to the study of Monney et al, cardiac MRI within 2 weeks of presentation is optimal in detecting diagnostically important evidence of myocardial damage (Monney et al., 2011). There will be a small number of patients (<10% of cases), where the cardiac MRI will demonstrate cardiac scarring that is more typical of CAD. According to the applicant, these patients will likely then proceed with some form of coronary imaging (cardiac CT) and corresponding interventions (Applicant, 2022a).

In the current clinical management pathway for diagnosing myocarditis in "ACS mimic" patients with high or intermediate pre-test risk of CAD, standard investigation tests (blood test, ECG, CXR ±TTE) were given to determine the likelihood of having CAD. For patients suspected with STEMI, has a high pre-test risk of CAD and haemodynamically unstable, ICA is used to diagnose obstructive CAD. For patients in the intermediate pre-test risk, CTCA is recommended as the initial test to diagnose obstructive CAD (Knuuti et al., 2020). However, ICA can also be done for CAD diagnosis confirmation or as an intervention. EMB is then performed for myocarditis diagnosis when obstructive CAD cannot be confirmed after CTCA or ICA. In the proposed pathway, when obstructive CAD cannot be confirmed, cardiac MRI is used to diagnose myocarditis. EMB is then given if a more specific diagnosis is required to guide myocarditis management.

For population 2, the algorithms were re-made based on the PASC's presentation (e.g. high and intermediate risk of CAD subgroups were added in). However, given the definition of the patient population requires further clarification as per PASC advice (as per PASC Outcome Number 1), the algorithms are subject to further change.

At its December 2022 meeting, PASC noted the applicant proposed an alternative clinical management algorithm that positioned cardiac MRI as a first line investigation instead of CTCA without the need to rule out obstructive CAD (due to the high pre-test probability of myocarditis in the revised population 2). The basis for the algorithm change were clinical guideline recommendations that differentiate high or intermediate ACS risk, and also the results of the CARMENTA trial. However, PASC noted that cardiac MRI was used as a 'gatekeeper' investigation to diagnose obstructive CAD rather than myocarditis in the CARMENTA trial, and thus queried the applicability of this trial population to the proposed revised population 2. The applicant explained that they mentioned the CARMENTA trial in their pre-PASC response to show that a non-invasive test such as cardiac MRI was safe and effective compared with an invasive test such as CTCA.

Proposed economic evaluation

The Applicant claims that cardiac MRI has a higher diagnostic accuracy (versus the comparator), leading to improved patient care and lower rates of inappropriate therapy (Applicant, 2022a). The Applicant notes that by achieving a more accurate diagnosis, it is expected that a greater number of patients will receive the appropriate therapy for myocarditis, leading to better resolution of symptoms and a lower incidence of potential lifelong anti-atherosclerotic therapies (Applicant, 2022a).

Furthermore, the Applicant claims that the safety profile of cardiac MRI is superior to current comparators such as EMB and ICA (Applicant, 2022a). The Applicant highlights that EMB carries a risk of vascular-access complications, malignant arrhythmia and cardiac perforation, while ICA carries a risk of heart attack, stroke, vascular-access complications and bleeding, arrhythmias, allergic reactions to dye, kidney injury or death (Applicant, 2022a).

Based on claims made by the Applicant and considering the matrix in Table 10, the most appropriate economic evaluation for both populations will be a cost-effectiveness analysis (CEA) or cost utility analysis (CUA).

Despite the intervention being claimed to lead to a greater number of patients receiving the appropriate therapy, myocarditis is a self-limiting disease, which may limit the benefit of cardiac MRI on long-term patient outcomes. Nevertheless, the accurate diagnosis of myocarditis may have additional non-health benefits associated with the value of knowing. Such value of knowing outcomes would be best incorporated into a cost-consequence analysis (CCA), presented to supplement a stepped CEA or CUA.

Table 10 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

Comparative		Comparative effectiveness		
Safety	**Inferior**	**Uncertain[a]**	**Noninferior[b]**	**Superior**
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain[a]	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior[b]	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	**CEA/CUA**

Abbreviations: CEA = cost-effectiveness analysis; CMA = cost-minimisation analysis; CUA = cost-utility analysis
? = reflects uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis
[a] 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations
[b] Adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

PASC noted that the claims are superior safety, superior diagnostic accuracy and superior patient outcomes. PASC noted that cardiac MRI may have limited benefit on long-term patient outcomes as myocarditis is usually a self-limiting disease. No changes to the proposal for a cost-effectiveness analysis / cost-utility analysis were noted by PASC.

Proposal for public funding

The Applicant has proposed the following MBS item for cardiac MRI based on the advice from PASC. Suggestions were made during the development of the PICO (in *italicised* text below).

The applicant's proposed fee for cardiac MRI was the same as the temporary MBS item for the diagnosis of mRNA-associated myocarditis (MBS item 63399), given that the cardiac MRI sequences performed for the proposed item are identical to those for the temporary one. The temporary service was introduced for cardiac MRI to assist in diagnosing myocarditis that may occur after vaccination with the mRNA COVID-19 vaccines Comirnaty (Pfizer) and Spikevax (Moderna). This service is available for use on an interim basis from 1 January 2022 to 31 December 2022. At the time the application was lodged, the fee for the temporary cardiac MRI item was $855.20, however the fee has since increased with indexation to $868.90. Therefore, the Department will continue with the economic evaluation of the proposed item based on the updated fee of $868.90.

The Applicant advises that most patients will only undergo a single cardiac MRI in a year, however in limited circumstances (e.g. those with cardiac dysfunction), some patients may require a follow-up scan to demonstrate resolution of inflammatory changes.

The Applicant acknowledges that where cardiac MRI replaces EMB (MBS item 38275, $310.25) there may be greater costs to the MBS; however, the Applicant claims that the higher cost may be offset in conditions where repeat EMB is indicated (Applicant, 2022a). On the other hand, other costs associated with EMB (e.g. anaesthesia service and histological tests for the sample costs) could also offset some of the proposed technology. The detailed cost items will be examined closed in the economic evaluation during the assessment phase.

The HTA group proposed item descriptor based on PASC advice (August 2022) is provided below:

Category 5 – DIAGNOSTIC IMAGING SERVICES – Group I5 – Magnetic resonance imaging
MBS item *XXXX Proposed item descriptor: MRI scan of cardiovascular system for the assessment of myocardial structure and function and characterisation, if the service is requested by a specialist or consultant physician who has assessed the patient, and the request for the scan indicates: (a) the patient has suspected myocarditis and would otherwise require endomyocardial biopsy to confirm the diagnosis; OR (b) the patient has suspected myocarditis and the results from the following examinations are inconclusive to form a diagnosis: (i) troponin, (ii) chest X-ray, (iii) transthoracic echocardiogram, and (iv) obstructive coronary artery disease has been excluded by computed tomography coronary angiography or invasive coronary angiography, or by stress testing (exercise ECG, stress echocardiography or stress myocardial perfusion imaging). (R) (Anaes.) (Contrast)
Fee: $868.90 Benefit: 75% = $651.70 85% = $781.00 Plus: GBCA MBS item 63491: Fee: $45.50 Benefit: 75% = $34.15 85% = $38.70

PASC agreed that the item descriptor should be modified to reflect the diagnostic pathways for the two proposed populations as discussed in the PICO. Thus, PASC advised that the 'exclusion of obstructive coronary artery disease' (by ICA or CTCA or other investigations) should be considered for inclusion in the item descriptor. PASC also advised that 'the patient has suspected myocarditis after receiving an mRNA COVID vaccine' should be removed given these individuals are already encompassed in population 1.

In addition, PASC also considered that 'specialist' should be added since that the service is requested by a specialist or consultant physician as in line with other reimbursed MRI MBS items.

PASC noted that the fee of standard item for GBCA (MBS item 63491) should also be included, given GBCA would be used as standard (unless contraindicated).

At its December 2022 meeting, PASC noted the applicant revised the proposed item descriptor to align with the revised definition for patients with intermediate ACS risk (patient population 2). This resulted in the removal of TTE as a prior test, and obstructive CAD no longer needing to be excluded by CTCA or ICA or other investigations. However, PASC noted that TTE was a relevant prior test for patients with acute onset cardiomyopathy (population 1) and thus queried whether there should be separate item descriptors for each population.

The applicant revised item descriptor presented to PASC (December 2022) is presented below:

Category 5 – DIAGNOSTIC IMAGING SERVICES – Group I5 – Magnetic resonance imaging

MBS item *XXXX Proposed item descriptor: MRI scan of cardiovascular system for the assessment of myocardial structure and function and characterisation, if the service is requested by a specialist or consultant physician who has assessed the patient, and the request for the scan indicates: (a) the patient has suspected myocarditis and would otherwise require endomyocardial biopsy to confirm the diagnosis; OR (b) the patient has suspected myocarditis and the results from the following examinations are inconclusive to form a diagnosis: (i) troponin, (ii) chest X-ray, (iii) *electrocardiogram*, and *(c) there are no high-risk features for coronary artery disease identified on clinical history, examination, or with the above investigations.* (R) (Anaes.) (Contrast)
Fee: $868.90 Benefit: 75% = $651.70 85% = $781.00 Plus: GBCA MBS item 63491: Fee: $45.50 Benefit: 75% = $34.15 85% = $38.70

Note the italicised text shows the amendments made to the updated population

Post the PASC meeting, the applicant after discussion with stakeholders, proposed a modified item descriptor which aimed to provide a more restrictive definition of population 2 for consideration of the PASC. *Out of session, PASC queried whether the item descriptor should also include a relevant clinical presentation:*

- *Acute onset (<3 months) of heart failure or unexplained arrhythmia (Population 1)*
- *Acute onset of chest pain suspected due to myocarditis (Population 2).*

Thus, PASC suggested the following changes for the applicant's proposed item descriptor which are presented in italicised text and strikethrough below. PASC also noted that the qualifier of 'high-risk features' implies an accepted definition, which could therefore be included in an explanatory note to reference definition in the NHF-CSANZ guidelines (although these are currently undergoing review).

Category 5 – DIAGNOSTIC IMAGING SERVICES – Group I5 – Magnetic resonance imaging
MBS item *XXXX Proposed item descriptor: MRI scan of cardiovascular system for the assessment of myocardial structure and function and characterisation, if the service is requested by a specialist or consultant physician who has assessed the patient, and the request for the scan indicates: (a) the patient has *acute onset (<3 months) of heart failure or unexplained arrhythmia* suspected *due to* myocarditis and would otherwise require endomyocardial biopsy to confirm the diagnosis; OR (b) the patient has *acute onset of chest pain* suspected *due to* myocarditis on the basis of*:* (i) Elevated troponin, OR (ii) Abnormal electrocardiogram, AND (iii) there are no ~~high-risk features for coronary artery disease~~ *other features of an acute coronary syndrome* identified on clinical history, examination, or with the above investigations. (R) (Anaes.) (Contrast)
Fee: $868.90 Benefit: 75% = $651.70 85% = $781.00 Plus: GBCA MBS item 63491: Fee: $45.50 Benefit: 75% = $34.15 85% = $38.70

Note the italicised text shows the amendments made to the updated population

Summary of public consultation input

Fifteen consultation surveys were received for August 2022 PASC consideration: five professional organisations, five individual medical professionals, one consumer organisation and one individual consumer. The organisations that submitted input were:

- Royal Australia and New Zealand College of Radiologists (RANZCR)
- Australian Diagnostic Imaging Association (ADIA)
- Society for Cardiovascular Magnetic Resonance (SCMR)
- The Australian Society of Medical Imaging and Radiation Therapy (ASMIRT)
- International Society for MR Radiographers and Technologists (ISMRT)
- Cardiomyopathy Association of Australia Inc. (Cardiomyopathy Australia)

The consultation feedback from professional and consumer organisations and individuals were all supportive of the application.

The consultation feedback consistently agreed with the clinical need and public health significance of publicly funding this application. Professionals highlighted:

- the improved safety compared to the comparator
- reduced need for downstream testing and less burden to society from undiagnosed myocarditis
- diagnostic certainty from excellent sensitivity and specificity of the proposed service
- improved equity of access to the proposed service with public funding by reducing financial driven restrictions

There was agreement from all health professionals that MRI was the most reliable non-invasive method of diagnosing myocarditis, with three specialists stating that CMR was the gold standard. As well as agreeing with the clinical need and public health significance, the consultation feedback ranged from agreeing to strongly agreeing with the proposed population, comparators and service descriptors and fees.

SCMR noted that experience from other healthcare systems, particularly in Europe and the US, shows that access to cardiac MRI will in most cases replace the use of these invasive procedures. They also note that reimbursing the proposed service will align medical practice in Australia with international guidelines and best medical practice internationally. An individual professional commented that in the last 10 years cardiac MRI was able to avoid biopsy in >95% of cases.

PASC noted that the consultation feedback was received from five professional organisations, five individual medical professionals, one consumer organisation and one individual consumer. The consultation feedback was generally supportive of the application.

Consultation feedback consistently raised concerns that cardiac MRI requires subspecialised training and equipment. Clarity regarding certification requirements for reporting and providing cardiac MRI may need to be considered to ensure safe, high-quality services. ISMRT stated that it is essential that cardiac imaging specialists providing cardiac MRI services in Australia are fellowship trained and credentialled in cardiac MRI as specified in the existing RANZCR/CSANZ training and credentialling frameworks. RANZCR agreed that the proposed service requires a similar level of skill as currently listed items 63388 and 63391. ASMIRT commented suggesting that providers be restricted similarly to MBS item number 63399. Their suggestion is that cardiac MRI can be provided by a person who is a specialist that is either a participant in the Royal Australian and New Zealand College of Radiologists' Quality and Accreditation Program or is recognised by the Conjoint Committee for Certification in Cardiac MRI. RANZCR expressed concern that the provider requirement of recognition by the Conjoint Committee in cardiac MRI will severely limit patient access and result in a serious underutilisation of the service.

Access to specialised equipment was also raised as a concern. ASMIRT stated that there are limited numbers of MRI machines to provide the proposed service and further suggested that this service be performed on both partially and fully Medicare-eligible MRI machines. SCMR stated that, in a survey conducted on 1000 international users of CMR, they found that one of the greatest barriers to CMR use is access to the technology.

PASC noted that, the provider requirement (recognition by the Conjoint Committee in Cardiac MRI) proposed in the application will limit patient access. This concern was raised by three professional medical organisations, including the Royal Australian and New Zealand College of Radiologists, the Australian Diagnostic Imaging Association, and the Australian Society of Medical Imaging and Radiation Therapy. It was noted that one piece of feedback was received from the Cardiomyopathy Association of Australia Inc. The feedback raised concerns about patient out-of-pocket costs and patient access to the service due to living in a regional or remote area.

Individual professionals raised concerns that the proposed service descriptor does not include the urgent requirement for patients referred by medical oncologists regarding immunotherapy induced myocarditis and that the true cost of the proposed service is closer to $900-$1000.

Two specialists noted that a cardiac MRI national database like NEDA would be of further benefit to public funding of the proposed service.

Among the individual feedback (6 cardiologists; 1 private individual [whose wife has cardiomyopathy due to cystic fibrosis and raised no concerns], two cardiologists raised a concern that the MBS fee may be too low. It was noted that, feedback from one cardiologist suggested that the proposed procedure was less complicated than the one for ARVC (MBS item 63395 and 63397). Feedback from three individual cardiologists and one private individual raised no concerns.

The Department requested further targeted consultation regarding the population for the proposed service provided. Targeted consultation feedback was received for December 2022 PASC consideration from the professional organisation SCMR and raised the following key points:

- Population 2 could be further defined by adequate clinical workup to exclude patients with a moderate-high likelihood of acute coronary syndrome (ACS) noting that:
    - Patients with a moderate-high likelihood of ACS should be considered for CMR if the ischemia work up is negative or equivocal
    - Patients with a similar likelihood of ACS versus myocarditis require clinical judgement and should be considered for CMR prior to ischemia work up if stable without ongoing chest pain – noting this may obviate the need for invasive testing
- Examples of when CMR is indicated for both population groups could not be refined solely by duration of symptoms. SCMR referred to the AHA 2020 Expert Consensus Document on Management of Acute Myocarditis and Chronic Inflammatory Cardiomyopathy to provide definitions of acute, chronic, and chronic inflammatory cardiomyopathy that included symptom duration.

In addition to the targeted feedback from SCMR, consultation feedback on the application was received from one consumer organisation the National Heart Foundation of Australia (the Heart Foundation). The consultation feedback received from the Heart Foundation was supportive of public funding for cardiac MRI in the diagnosis of myocarditis, strongly agreeing with the clinical claim, proposed population, and proposed comparators. The Heart Foundation reiterated that cardiac MRI is the gold standard to diagnose myocarditis and noted that patients should be seen by a multidisciplinary team, and that a lack of equity of access to the proposed testing may occur outside major cities.

Next steps

At its December 2022 meeting, PASC noted the applicant agreed to try and define population 2 more narrowly with the revision to be incorporated into the PICO out of session. PASC emphasised that the further refinement of population 2 needs to be considered in the context of how CMR would change patient management in that specific context.

Applicant Comments

We had made note in the December MSAC PASC meeting that the cost of endomyocardial biopsy (EMB) was more than simply the cost of the Medicare item number for this procedure, as patients undergoing EMB required admission to hospital as a day procedure as well as time allocated in the cardiac catheter lab. This does not appear to have been noted in the current PICO and we believe this cost is an important consideration with respect to population 1.

Following the MSAC PASC meeting in December we (the applicant) forwarded a suggested modified item descriptor that we believed would more tightly define the population group (hence preventing leakage) whilst capturing the vast majority of patients in whom acute myocarditis was likely to be present. We note that the PICO now includes a revised item number descriptor based on our suggestions.

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Clinical management algorithms by the Applicant

Figure 7 **Current clinical management algorithm for population 1**

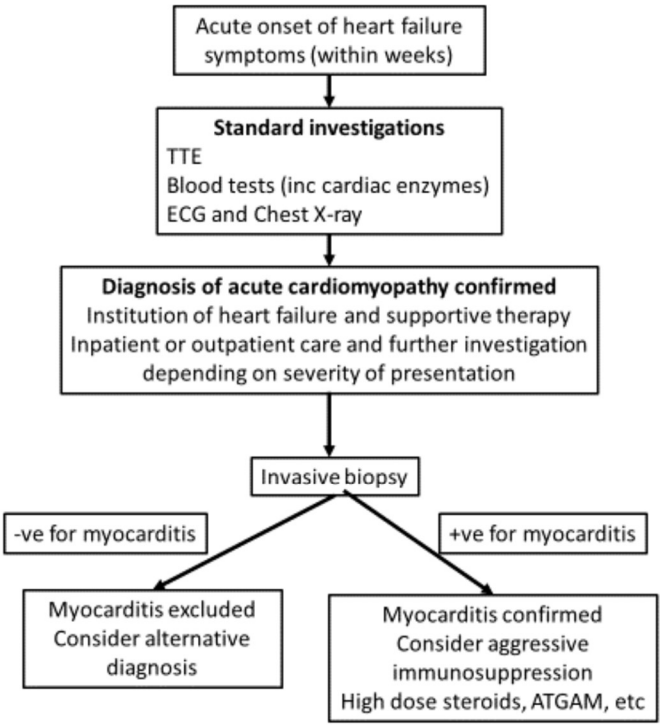

Figure 8 **Proposed clinical management algorithm for population 1**

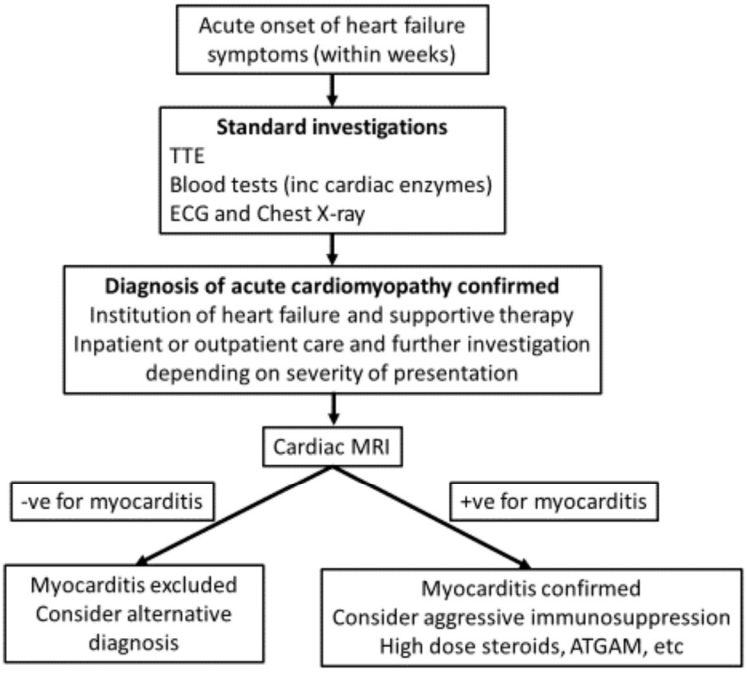

Figure 9 Current clinical management algorithm for population 2

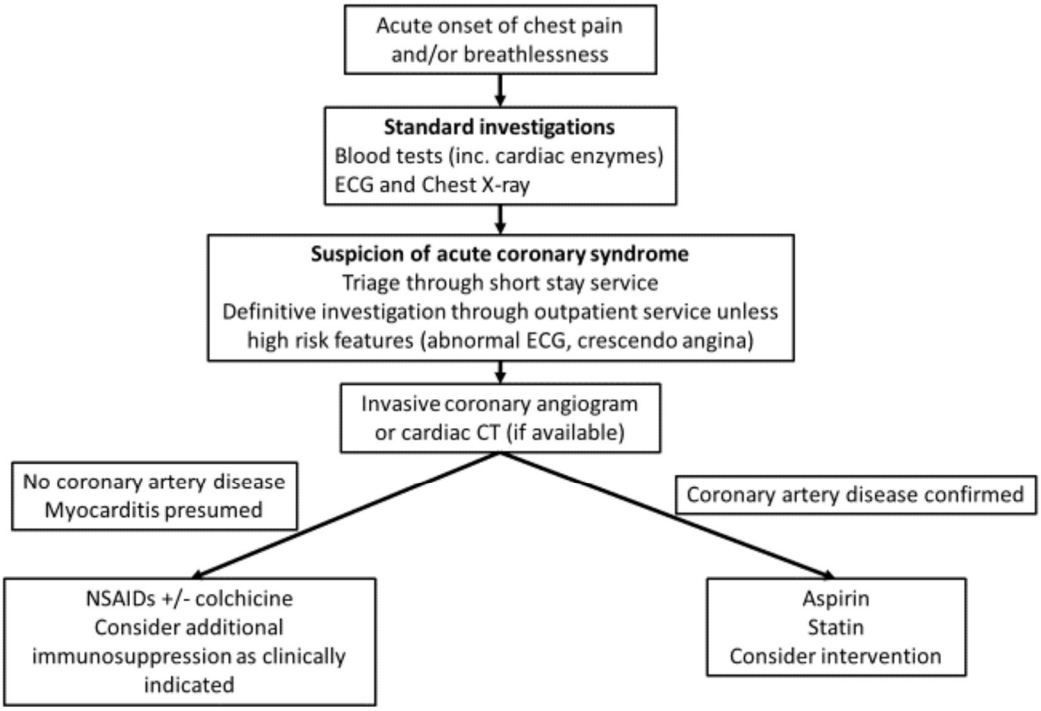

Figure 10 Proposed clinical management algorithm for population 2