

Review

High-sensitivity troponin in chronic kidney disease: Considerations in myocardial infarction and beyond

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Acute myocardial infarction (MI) represents one of the most common hospital encounters, with significant short-term and long-term morbidity and mortality, and frequently occurs in patients with chronic kidney disease (CKD). Cardiac troponin is an exquisitely sensitive biomarker for myocardial injury and plays an essential role in the diagnosis, risk-stratification, and management of MI. In 2017, the United States Food and Drug Administration approved Roche Diagnostics' 5th generation high-sensitivity cardiac troponin (hs-cTn) for clinical use. Whilst the improved analytical sensitivity of these new high-sensitivity troponin assays facilitate early diagnosis of MI, it also frequently identifies troponin elevations above the conventional reference threshold in the context of non-coronary conditions such as renal dysfunction, and can represent a major diagnostic challenge to clinicians. Furthermore, the optimal management strategy of patients with troponin elevation and high comorbidity burden, a common issue in patients with CKD, remains undefined. In recent years, there has been substantial research and progress undertaken in this rapidly evolving area. In this review, we aim to provide clinicians with an overview of hs-cTn in the setting of CKD as well as an update on its application and the particular considerations involved in the management of myocardial infarction, stable coronary artery disease and myocardial injury in this high risk population.

Keywords

High-sensitivity troponin; chronic kidney disease; coronary artery disease; myocardial injury; dialysis

1. Introduction

Acute myocardial infarction (MI), which is most commonly due to atherosclerotic coronary artery disease (CAD), is still the major cause of cardiovascular mortality and morbidity worldwide (Benjamin et al., 2019). Despite our best attempts to manage CAD and its lethal sequelae with implementation of current published guidelines, patients with chronic kidney disease (CKD) continue

to be disproportionately affected by cardiovascular disease compared to those without renal impairment (Culleton et al., 1999; Go et al., 2004; Iwagami et al., 2018; Matsushita et al., 2010).

Following the joint recommendation by the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) in 2000, cardiac troponin (cTn) emerged as the biomarker of choice for myocardial injury and plays an essential role in the diagnosis of MI (Alpert et al., 2000; Amsterdam et al., 2014; Chew et al., 2016; Ibáñez et al., 2017). In 2010, the first 5th generation high-sensitivity cTn (hs-cTn) assays became commercially available, and it subsequently received approval for clinical use by the United States Food and Drug Administration (FDA) in 2017 (US FDA, 2017). Its superior precision and sensitivity facilitates early diagnosis of MI, however, it also posed unique challenges to clinicians as it identifies elevated troponin levels above the conventional reference threshold in over 50% of patients with renal dysfunction and final admission diagnoses other than acute MI (Chen et al., 2013; Flores-Solís and Hernández-Domínguez, 2014; Pfortmueller et al., 2013; Twerenbold et al., 2015). Furthermore, troponin levels have also been shown to increase in a non-linear manner as renal function deteriorates; making the interpretation of elevated troponin levels in patients with CKD and suspected CAD even more difficult (Chesnaye et al., 2019). The Fourth Universal Definition of MI consensus was subsequently published in 2018 to address these challenges (Thygesen et al., 2018). However, the optimal management strategy of patients with both CAD and CKD is difficult given that they are more likely to have higher comorbidities, present with atypical symptoms (Herzog et al., 2007; Sosnov et al., 2006), and more prone to adverse events following intervention (Chuang et al., 2018).

This review aims to provide an overview of hs-cTn with a particular focus on patients with CKD. It will also provide a clinically focused update on the application of hs-cTn as well as considerations involved in the assessment and management of myocardial infarction, stable CAD and myocardial injury in this high risk population.

2. Cardiac troponin and fifth-generation high-sensitivity troponin assays

Cardiac troponin is an extremely sensitive biomarker for myocardial injury and is the current biomarker of choice for the diagnosis, risk-stratification, and clinical management of MI (Amsterdam et al., 2014; Ibáñez et al., 2017; Thygesen et al., 2018, 2010). In brief, cTn is a complex of three regulatory proteins (troponin I, troponin C and troponin T) that is bound to tropomyosin on the actin filament within cardiac sarcomere. In a resting cardiac myocyte, the troponin complex blocks the binding site for myosin on the actin filament. When an action potential triggers an increase in intracellular Ca^{2+} concentration, a conformational change in the troponin complex occurs, resulting in the unblocking of tropomyosin from the myosin binding site on the actin filament. This allows myosin to bind to actin, which results in myocyte contraction (Takeda et al., 2003). Approximately 92-95% of cellular troponin is bound as a constituent of the troponin-tropomyosin-actin complex within the cardiac sarcomere with the other 5-8% unbound in the myocyte cytoplasm (Takeda et al., 2003). This free, unbound troponin constitutes the 'early releasable troponin pool.' It is thought that a small amount of cTn is released immediately following myocyte injury from this pool and, with normal renal function, would be cleared rapidly as the plasma half-life of troponin is 2 hours (Fridén et al., 2017; Gerhardt et al., 1991). If significant myocyte injury or destruction occurs, the structurally bound troponin is released in a gradual fashion, causing a more sustained troponin release. Although the exact mechanisms by which troponin is eliminated from the body remains to be fully elucidated, it is hypothesised that troponin is cleared, at least in part, by the renal reticuloendothelial system (Fridén et al., 2017; Takeda et al., 2003). It is important to note that whilst troponin is a useful marker of myocardial injury, it does not inform the underlying aetiology of the damage nor does it confirm myocyte necrosis. At least five other mechanisms of cTn release on a cellular level have been described other than myocyte necrosis, predominantly from the early releasable troponin pool, including membranous blebs, increase membrane permeability, proteolytic fragmentation, apoptosis and normal cell turnover (Garg et al., 2017). Clinically, this simply means that troponin elevations can have mechanisms other than ischemia, which is now formally termed 'myocardial injury' (Thygesen et al., 2018). These non-necrosis related release mechanisms coupled with impaired renal clearance underpins the challenges associated with interpreting troponin elevations in patients with CKD.

In 2010 and 2012, a new generation (5th generation) of troponin was made commercially available – high-sensitivity troponin-T and troponin-I, respectively (Apple et al., 2012, 2017). Broadly, these new assays use mouse-human chimeric detection antibodies with optimised buffer that decreased background noise thereby improved noise-to-signal ratio (Giannitsis et al., 2010). These 5th generation assays are defined by their superior precision, as measured by their coefficient of variation (CV%), compared to the previous generation assays. Coefficient of variation, defined as the ratio of the standard deviation to the mean multiplied by 100, is a standardised measure of frequency distribution and is widely used in analytical chemistry to express the precision and repeatability of an assay. In simple terms, the smaller the CV%, the more

Table 1. Non-traditional factors associated with adverse cardiac events in patients with renal impairment

- Abnormal phosphate, calcium, and parathyroid hormone metabolism (Hruska et al., 2011; Kestenbaum et al., 2005)
- Modification of lipoproteins, including low-density lipoprotein carbamylation, modified apolipoprotein isoforms (Kaysen, 2009a,b)
- Systemic inflammation (Russa et al., 2019; Santoro, 2002)
- Oxidative stress and endothelial dysfunction (Nuhu and Bhandari, 2018)
- Albuminuria (Kendrick and Chonchol, 2008)
- Hyperhomocysteinaemia (Ganguly and Alam, 2015)
- Anaemia (Vlagopoulos et al., 2005)

precise an assay is. These 5th generation assays are defined by having a CV% of less than 10 at the 99th centile upper reference limit (URL), whereas the previous generation assays ranged between 10-20% (Apple et al., 2017). The use of hs-cTn assays that are more precise, defined as having CV% of < 10% at the 99th percentile URL, makes the interpretation of a significant serial change less challenging without increasing the false positive rate (Thygesen et al., 2018). Thus, whilst prior assays with CV% between 10% to 20% are deemed acceptable for clinical use, the improved precision of hs-cTn allows for quantification of lower levels of troponin and detection of interval change with greater confidence. Since its introduction, hs-cTn has been used in routine clinical practice in Europe, Asia, and Australia; with the United States being the latest country to take up the assay with FDA approval of high-sensitivity troponin-T (hs-TnT) in 2017 (US FDA, 2017). The 99th centile URL set by the FDA were 19 ng/L for both genders; or 14 ng/L for females and 22 ng/L for males. This has since been followed by the recent FDA approval of high-sensitivity troponin-I (hs-TnI) by Architect Stat (Abbott Laboratories) in September 2019 (US FDA, 2019).

3. Pathophysiology of accelerated coronary artery disease in patients with chronic kidney disease

It has been well described in both population-level observational (Bundy et al., 2018; Manjunath et al., 2003) and pathological studies (Nakamura et al., 2009; Nakano et al., 2010; Schwarz et al., 2000) that there is an inverse relationship between eGFR and the prevalence of epicardial vessel atherosclerosis, microvascular and macrovascular calcification, myocardial fibrosis. Complex interactions between traditional cardiovascular risk factor and non-traditional CKD-specific factors contribute to this phenomenon. Some of the non-traditional CKD-specific factors that are associated with adverse cardiac events are listed in Table 1. It is likely that both accelerated micro/macro CAD and non-traditional risk factors contribute to non-infarct related troponin elevations that are commonly seen in this patient cohort (Kendrick and Chonchol, 2008; Subbiah et al., 2016; Unger et al., 2016). However, the exact mechanisms and the relative contribution of each remain to be quantified. More detailed reviews of CKD-specific pathophysiology can be found elsewhere (Kendrick and Chonchol, 2008; Schiffrin et al., 2007; Subbiah et al., 2016; Yerkey et al., 2004).

There are two main clinical implications for patients with CKD

that needs to be considered. Firstly, the profoundly different pathophysiology of cardiovascular disease in CKD patients, especially those on dialysis, translates to modified efficacy of therapies that have proven benefit in non-CKD patients. Secondly, patients who were previously thought to have 'type 2 MI' or 'silent MI' may now be reclassified as 'myocardial injury' using the new Fourth Universal Definition (see below) (Thygesen et al., 2018). As a consequence, their outcomes may not respond to therapies targeted at traditional ischaemic risk factors.

4. Myocardial infarction, myocardial injury and the Fourth Universal Definition of myocardial infarction

The improved analytical precision of the 5th generation troponin facilitates earlier diagnosis of MI due to its ability to more precisely detect lower levels of troponin and interval changes (Thygesen et al., 2018). This led to the recommendation of accelerated protocols by the 2015 ESC guidelines in the assessment of patients with suspected MI based on data from prospective observational studies (Roffi et al., 2015). These protocols shorten the time of repeat troponin testing from 3-6 hours (Thygesen et al., 2012) to 0-2 hours (Lindahl et al., 2016; McRae et al., 2017). In 2019, a 1-hour protocol was validated in the only randomised trial to date (Chew et al., 2019), which demonstrated non-inferiority to standard-of-care for safety outcomes with reduced emergency department length of stay and subsequent hospital admission (Thygesen et al., 2010). However, these assays come with new challenges including increased identification of troponin elevations above the conventional reference threshold in patients without objective evidence of myocardial ischaemia (Chew et al., 2019; Shah et al., 2018). This is especially relevant to patients with CKD given that more than 50% are observed to have elevated high sensitivity troponin levels above this 99th percentile threshold (Twerenbold et al., 2015).

To address these concerns, the Fourth Universal Definition of MI consensus document, endorsed by both the ESC and ACC, was published in 2018 (Thygesen et al., 2018). It is the first guideline to formally define this syndrome as 'myocardial injury' and distinguish it from MI. It outlined three main patterns of troponin elevation - acute MI, acute myocardial injury and chronic myocardial injury. Acute MI is defined as myocardial injury with clinical evidence of myocardial ischaemia and can be subdivided into five types: type 1 (atherosclerotic plaque rupture), type 2 (supply-demand mismatch), type 3 (cardiac death prior to availability of troponin results), type 4 (percutaneous coronary intervention [PCI]-related), and type 5 (cardiac surgery-related) (Thygesen et al., 2018). In contrast, myocardial injury is defined as an elevated troponin without evidence of myocardial ischaemia and is subdivided into acute and chronic injury depending on the presence or absence of an observed rise and/or fall in troponin levels, respectively (Thygesen et al., 2018). In patients with CKD, acute and chronic myocardial injury likely account for a substantial portion of troponin elevations (Janzon et al., 2016; Lambrakis et al., 2019; Taylor et al., 2007; Thygesen et al., 2010). Indeed, in two recent large randomised trials of hs-cTn in clinical practice involving 48,282 and 3,378 patients both acute and chronic myocardial injury was found to account for at least 30% of patients with ele-

vated troponin (Chew et al., 2019; Shah et al., 2018). In addition to reduced renal troponin clearance, other proposed mechanisms of 'non-plaque rupture' causes of troponin elevation in patients with CKD include increased ventricular pressure, small vessel coronary obstruction, supply-demand mismatch, left ventricular hypertrophy, and uraemia (Gualandro et al., 2012). Specific to patients on dialysis, intra-dialytic hypotension and myocardial stunning may also cause myocardial injury (Burton et al., 2009; Stefánsson et al., 2014). As a result, diagnosing MI in patient with CKD can be challenging if symptoms, ECG or imaging changes indicating ischaemia are atypical (Herzog et al., 2007; Sosnov et al., 2006) or if the patient presents late after onset of chest pain.

In the clinical assessment of CKD patients presenting with suspected MI and elevated troponin, the two priorities are: (1) the accurate and timely diagnosis of MI and (2) decision for subsequent down-stream investigation and management of patients with myocardial injury when MI has been excluded. In the following sections, we will provide an overview of the current evidence on the investigation and management of patients with CKD in: (1) acute MI, (2) stable coronary artery disease and (3) myocardial injury.

5. Assessment and management considerations in patients with chronic kidney disease

5.1 Acute myocardial infarction

Assessment and management of CKD patients with acute MI come with unique challenges including altered diagnostic performance of hs-cTn algorithms, high likelihood of pre-existing comorbidity burden, atypical presenting symptomatology (Herzog et al., 2007; Sosnov et al., 2006), higher risk of complications associated with intervention (Chuang et al., 2018) and increased bleeding and ischaemic risk (Chew et al., 2016).

The diagnostic performance of hs-cTn in the assessment of CKD patients presenting with suspected MI has been evaluated in three prospective, adjudicated, observation studies (Gunsolus et al., 2018; Miller-Hodges et al., 2018; Twerenbold et al., 2018). Twerenbold et al. (2018) compared the diagnostic performance of the 0/1-hour ESC algorithms of rapid rule-in and rule-out in patients with and without renal dysfunction using both hs-TnT and hs-TnI. The authors reported that whilst the incidence of acute MI were higher in patient with renal impairment (31% vs. 13%), the specificity was significantly lower (hs-TnT: 88.7% vs. 96.5%; hs-TnI: 84.4% vs. 91.7%) with sensitivity remaining relatively unchanged (hs-TnT: 100.0% vs. 99.2%; hs-TnI: 98.6% vs. 98.5%). Furthermore, the efficacy (those successfully triaged as rule-in or rule-out) of the 0/1-hour algorithm was much lower in patients with renal impairment due to fewer patients fulfilling rule-out criteria (51.3-53.5% vs. 76.1-81.2%). Interestingly, the authors found that there no clinically significant difference between the hs-TnT and hs-TnI assays and that the overall safety and efficacy could not be significantly improved by simply changing the troponin cut-off. In another study by Gunsolus et al. (2018) using hs-TnI, the authors reported a similar incremental increase in MI diagnosis (7% in patient with normal renal function vs. 21% in patient with GFR < 30ml/min/1.73m²) and reduction in specificity (91-96% in patient with normal renal function vs. 42-74% in patient with GFR < 30ml/min/1.73m²) with worsening renal function, whilst sensi-

tivity and negative predictive value (NPV) were maintained. The study also showed that hs-TnI identified over 90% of MI within 3 hour. Similar findings were also observed in another study by Miller-Hodges *et al.* (2018) in 2018 using hs-TnI. All three studies confirmed the short and medium prognostic value of hs-cTn beyond diagnostic performance. In summary, what these studies inform us about the role of hs-cTn in the assessment of patients with CKD are: 1) pre-test probability of MI increases with worsening renal function, 2) hs-cTn assays are safe as part of accelerated MI rule-out protocols, 3) there is an incremental reduction in specificity and PPV (positive predictive value) of hs-cTn as renal function declines, and 4) hs-cTn remains a valuable tool for prognostic stratification. The optimal initial hs-cTn-based diagnostic algorithm and subsequent investigations remains to be determined. Practically, in patients with low-moderate cTn elevations, serial repeated testing for a rise and fall in troponin levels would be beneficial as a single elevated hs-cTn could be due to chronic myocardial injury (Januzzi *et al.*, 2019b). Patients with moderate-high levels of troponin elevation or high-risk features (see below) may be considered for invasive angiography given the high pre-test probability, difficulty of obtaining diagnostic certainty and prognostic impact of hs-cTn (deFilippi and Herzog, 2017; Gunsolus *et al.*, 2018; Miller-Hodges *et al.*, 2018; Twerenbold *et al.*, 2018). The above approach is based on individual conclusions made by the authors and not intended to be viewed as official recommendations.

Current guidelines recommend aspirin, P2Y12 inhibitor, hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor and invasive management with angiogram and subsequent PCI if appropriate, as treatment of choice for patients with acute MI (Amsterdam *et al.*, 2014; Chew *et al.*, 2016; Ibáñez *et al.*, 2017; Patel *et al.*, 2017b). However, these recommendations are based on clinical trials that were performed on highly selected patient groups with only marginal representation of CKD and dialysis patients (Damman *et al.*, 2011; Fox *et al.*, 2010; Henderson *et al.*, 2015; Wallentin *et al.*, 2009, 2016; Wasilewski *et al.*, 2015). In this section, we will provide an overview of the current evidence base for the management of acute MI in patients with CKD.

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor form the cornerstone of acute MI management and is universally recommended by all published guidelines despite no dedicated trials performed in patients with CKD (Amsterdam *et al.*, 2014; Chew *et al.*, 2016; Ibáñez *et al.*, 2017) (Table 2). Hs-cTn has been suggested to predict the efficacy of ticagrelor versus clopidogrel. In a sub-study of the PLATO trial, Wallentin *et al.* reported that ticagrelor was associated with a lower rate of cardiovascular death, myocardial infarction and stroke compared to clopidogrel in patients with high-sensitivity troponin-T ≥ 14.0 ng/L but not in patients with levels < 14.0 ng/L (Wallentin *et al.*, 2014). However, ticagrelor is not recommended in patients with stage 5 CKD or dialysis given the lack of safety data (Chew *et al.*, 2016; Ibáñez *et al.*, 2017). Current guidelines recommend 12 months of DAPT followed by aspirin monotherapy after acute MI. However, there are limited data to guide the optimal duration of DAPT and the choice of subsequent monotherapy in patients with CKD owing to increased ischaemic and bleeding risks (Chew *et al.*, 2016). Several large randomised trials have tested different combinations of shorter DAPT regimens (1-3 months) (Feres, 2013; Hahn *et al.*,

2019; Kim *et al.*, 2012; Mehran *et al.*, 2019; Valgimigli *et al.*, 2012; Vranckx *et al.*, 2018; Watanabe *et al.*, 2019), longer DAPT regimens (12 versus 30 months) (Kereiakes *et al.*, 2015) and choice of subsequent monotherapy (Hahn *et al.*, 2019; Mehran *et al.*, 2019; Vranckx *et al.*, 2018; Watanabe *et al.*, 2019). Two recent large-scale randomised trial should be noted – the 2019 TWILIGHT (Mehran *et al.*, 2019) and 2018 GLOBAL LEADERS (Vranckx *et al.*, 2018) trials with CKD patients accounting for approximately 17% and 30% of the patients in these trials, respectively. The TWILIGHT trial compared three months of DAPT followed by ticagrelor monotherapy with twelve months of DAPT in 7,119 patients (Mehran *et al.*, 2019). Interestingly, this trial selected for patients with increased bleeding risk with CKD being one of the considered risk factors. It demonstrated that shorter DAPT was associated with reduced bleeding with no increase in ischaemic events. However, comparable reduced bleeding risk with shorter DAPT was not seen in the GLOBAL LEADERS trial, involving 15,968 patients, that compared standard of care (DAPT for 12 months followed by aspirin for 12 months) with DAPT for 1 month followed by ticagrelor monotherapy for 23 months (Vranckx *et al.*, 2018).

Detailed review of the role of invasive management in patients with CKD and MI is beyond the scope of this review. In brief, there are limited data regarding the relative harms and benefits. Observational studies report reduced expected net benefit compared to patients without CKD largely due to the greater likelihood of competing risks including bleeding, recurrent ischaemic events, peri-procedural complications (e.g. contrast nephropathy, vascular complication; see Fig. 1) (Chuang *et al.*, 2018; Shaw *et al.*, 2016). Whilst observational studies have reported equivocal results, no survival benefit has ever been demonstrated in randomised trials involving patients with stage 3-5 CKD enrolled to routine early invasive approach (Charytan *et al.*, 2009). Those that may likely to benefit from early invasive management (+/- revascularisation) are patients who present with ST-elevation myocardial infarction, cardiogenic shock, and high-risk features; such as persistent pain, clinical heart failure and dynamic ECG changes (Patel *et al.*, 2017a).

Pre-hydration with normal saline, minimise contrast volume and use of low- or iso-osmolar contrast media are recommended for patients who proceed with invasive management by current guidelines (Chew *et al.*, 2016; Khwaja, 2012; Owen *et al.*, 2014; Windecker *et al.*, 2014). Several pharmacological interventions for the prevention of contrast-induced nephropathy in high-risk patients have shown inconsistent results in randomised trials and meta-analyses (Patschan *et al.*, 2018; Sharp *et al.*, 2019), including N-acetylcysteine (NAC), bicarbonate, statin, trimetazidine and nicorandil. The PRESERVE trial, published in 2018, is the largest randomised trial to-date that compared oral NAC and intravenous sodium bicarbonate against placebo (intravenous 0.9% sodium chloride) in 4,993 patients with stage 3 and 4 CKD undergoing coronary angiography (Weisbord *et al.*, 2018). The trial reported that there was no benefit of NAC or sodium bicarbonate for the prevention of need for dialysis or persistent decline in renal function at 90 days. As such, these pharmacological interventions have only received weak or are not recommended by current guidelines (Khwaja, 2012; Owen *et al.*, 2014; Windecker *et al.*, 2014). Lastly, the method of revascularisation (surgical versus percutaneous) as

Table 2. Recommended dosages of antiplatelet and anticoagulation therapies in acute myocardial infarction. Table adapted with permission from Chuang et al. (Boland and Muller., 2019; Jolly et al., 2017; Russo et al., 1995)

Antiplatelet therapies			
	Standard dose	Stage 4 CKD (estimated glomerular filtration rate 15-30 ml/min/1.73 m ²)	Stage 5 CKD (estimated glomerular filtration rate < 15 ml/min/1.73 m ²)
Aspirin	Initial dose of 150-300 mg orally followed by a maintenance dose of 75-100 mg/day	No adjustment required	No adjustment required
Ticagrelor	Initial dose of 180 mg orally, followed by a maintenance dose of 90 mg twice per day	No adjustment required	Not recommended
Prasugrel	Initial dose of 60 mg orally, followed by a maintenance dose of 10 mg/day If body weight < 60 kg, reduce maintenance dose to 5 mg/day Contraindicated if previous stroke/transient ischemic attack	No adjustment required	Not recommended
Clopidogrel	Initial dose of 600 mg orally followed by a maintenance dose of 75 mg/day	No adjustment required	No information available
Abciximab	Bolus of 0.25 mg/kg intravenously and 0.125 microg/kg/min infusion for 12 hours	Caution; consider bleeding risk	Caution; consider bleeding risk
Eptifibatide	Double follow of 180 microg/kg intravenously (10 minute interval) followed by an infusion of 2 microg/kg/min for up to 18 hours	Reduce infusion dose to 1 ug/kg/min	Not recommended
Tirofiban	25 ug/kg over 3 minutes intravenously followed by a maintenance infusion of 0.15 microg/kg/min for up to 18 hours	Reduce infusion rate to 50%	Not recommended
Anticoagulant therapies			
Unfractionated heparin	70-100 IU/kg intravenous bolus with no glycoprotein IIb/IIIa inhibitors 50-70 IU/kg intravenous bolus with glycoprotein IIb/IIIa inhibitors	No adjustment required	No adjustment required
Enoxaparin	1 mg/kg subcutaneously or 0.5 mg/kg intravenously followed by 1 mg/kg twice a day	1 mg/kg per day	Not recommended
Bivalirudin	0.75 mg/kg intravenous bolus with 1.75 mg/kg/hr infusion for up to 4 hours following the procedure	Reduce infusion rate to 1 mg/kg/hr	Reduce infusion rate to 0.25 mg/kg/hr

well as the best vascular access site (radial versus femoral in patients who may require radial access for arteriovenous fistula) remains to be determined (Sarnak et al., 2019).

In summary, given the complexity and potential multiple competing risks, an individualised approach with close consultation between cardiac and renal services centred around the patient's own preference should be the default strategy when managing acute MI in a patient with CKD.

5.2 Stable coronary artery disease

Given the high pre-test probability of CAD (Bansal et al., 2017; Matsushita et al., 2013), higher likelihood of atypical presentation (Schmidt et al., 2001) and high burden of competing pathologies (Arroyo-Espliguero et al., 2004; Matsushita et al., 2013), a high index of suspicion and care should be maintained when assessing CKD patient with suspected CAD (Knuuti et al., 2020).

Non-invasive testing is the most appropriate initial assessment for majority of CKD patients with symptoms suspicious of stable CAD. Three broad categories of coronary assessment that are com-

monly used in patients with CKD include: 1) non-invasive functional testing, 2) non-invasive anatomical testing with CT coronary angiography (CTCA) and 3) invasive coronary angiography. In addition to pre-test probability and diagnostic accuracy, selection of appropriate testing depends on exercise capacity (exercise ECG and echocardiography not appropriate if target exercise time and heart rate cannot be achieved), baseline ECG changes (exercise ECG contraindicated if pre-existing ST change or left bundle branch block), local availability of tests and contradictions to pharmacological or contrast agents. It has been described that functional testing in CKD has reduced accuracy with higher rate of both false-positive and false-negative due to factors such as reduced exercise capacity (e.g. due to anaemia, muscle fatigue, peripheral), pre-existing ECG changes and baseline left ventricular hypertrophy (Knuuti et al., 2020; Wang et al., 2011b; Winther et al., 2015a). In a Cochrane review of functioning testing for transplant candidates, the estimated sensitivity and specificity for myocardial perfusion scintigraphy was 0.74 and 0.7, respectively, whereas dobu-

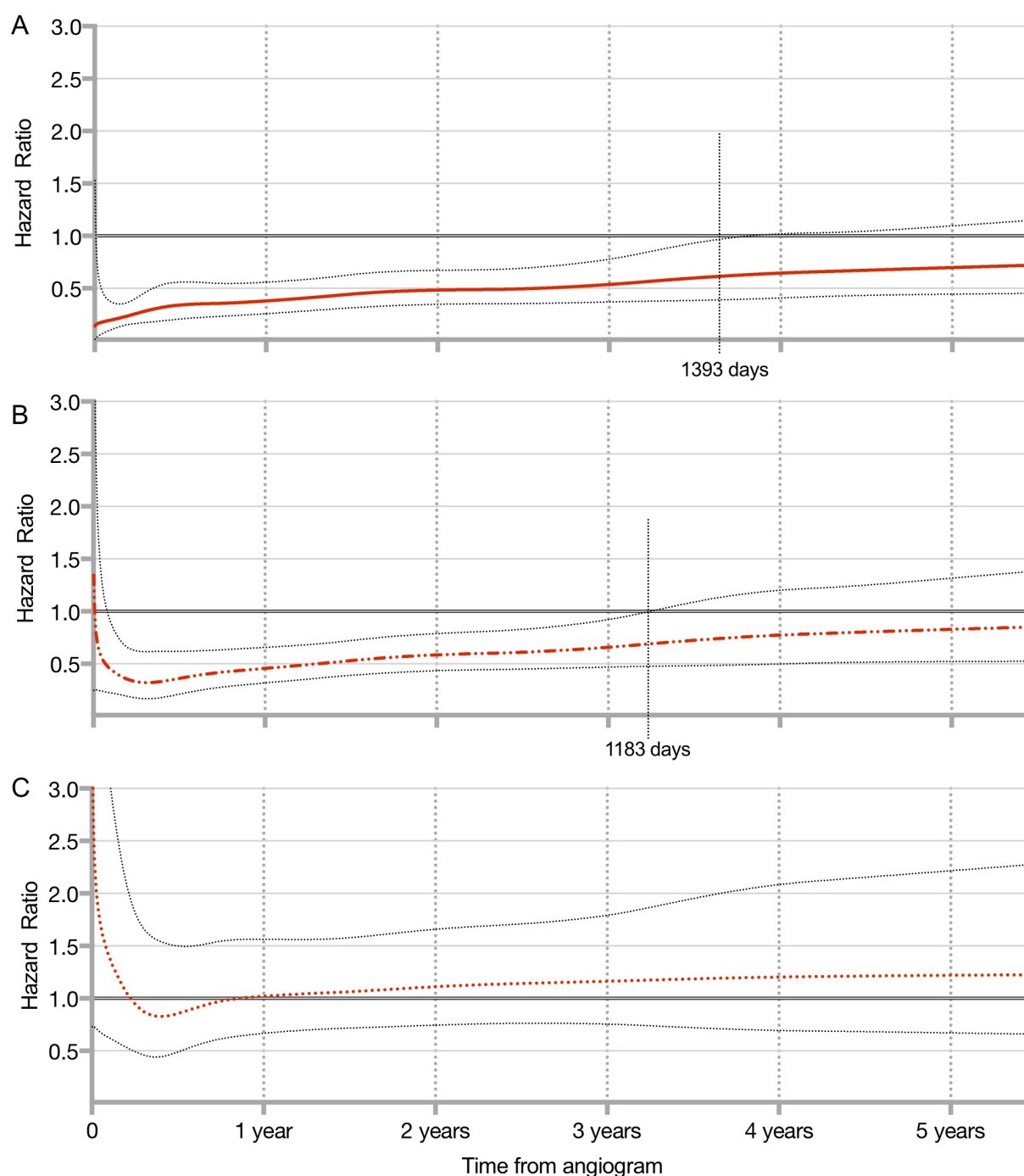


Figure 1. Effect of non-cardiac co-morbidity burden on the overall mortality benefit from invasive management in patients with (A) low non-cardiac comorbidity burden, (B) medium non-cardiac comorbidity burden, and (C) high non-cardiac comorbidity burden, derived from a cohort of 3,057 patients with elevated troponin (Chuang et al., 2018). Figure replicated with permission from Chuang et al.

tamine echocardiography was 0.79 and 0.89, respectively (Wang et al., 2011a). Therefore, in the presence of a negative functional test, ongoing risk factor modification and careful reassessment if symptom persists is critical. In comparison, CTCA may offer superior diagnostic accuracy compared to functional testing. In a study of 138 transplant candidates, CTCA was shown to have superior sensitivity (93% vs. 53%) and NPV (97% vs. 86%) for obstructive CAD compared to SPECT imaging (Winther et al., 2015a). Fur-

thermore, CTCA was also shown in this study to have similar PPV (41% vs. 44%) and modest specificity (63% vs. 82%) for obstructive CAD when compared to SPECT imaging (Winther et al., 2015a). The risk of contrast induced nephropathy needs to be considered, particularly in late-stage CKD. However, a small study of pre-dialysis transplant candidates reported that renal function largely returns to baseline with very low risk of requiring dialysis after CTCA (Winther et al., 2015b). Subsequent functional imag-

ing for inducible myocardial ischaemia is recommended if CTCA shows CAD of uncertain functional significance.

High-sensitivity troponin testing in the setting of suspected stable CAD has reported benefits in risk stratification in numerous studies (Adamson et al., 2017; Everett et al., 2015; Januzzi et al., 2019a; Omland et al., 2013). The study by Adamson et al. (2017) reported that each 2 fold increment in high sensitivity troponin-I was associated with a 1.71 fold increase in the odds of detecting obstructive CAD on CTCA. Furthermore, the addition of hs-TnI to the CADC (Coronary Artery Disease Consortium) risk model yielded a 10.5% reduction in the number patients without obstructive CAD on CTCA that were initially deemed to be at intermediate-high risk (Adamson et al., 2017). Relevant to treating clinicians, it was reported in this study that 21 troponin tests would be required to avoid one unnecessary CTCA. Unfortunately, studies reporting the benefit of hs-cTn testing in the setting of stable CAD and CKD is limited. A study of 1,864 patients with low-intermediate pre-test probability for stable CAD reported that both hs-TnT and hs-TnI remained a significant prognostic marker for adverse events, including death and MACE (major adverse cardiovascular events), even after adjusting for renal function (Cardinaels et al., 2016). Specifically, patients with elevated hs-TnT and hs-TnI were 3 and 8 times, respectively, more at risk for adverse events than those without troponin elevations. Relevant to patients with CKD, renal function was found to modify this association with increases in hs-TnT having 4 times more risk for adverse events in patients with reduced renal function than those with normal renal function (Cardinaels et al., 2016).

In managing patients with stable CAD, the two key objectives are: 1) relieve symptoms of myocardial ischaemic and 2) improve prognosis. In the general population, there is relative robust evidence supporting the use of optimal medical therapy (OMT) as the foundation of treatment with revascularisation as an adjunct (Knuuti et al., 2020). However, in CKD, there is limited evidence to guide medical therapy or revascularisation given the lack of representation in clinical trials. (Sarnak et al., 2019; Wasilewski et al., 2015). For lipid-lowering therapy, the net ischemic benefit with statin-based therapy appear to decrease as the estimated glomerular filtration rate (eGFR) declines (Messow and Isles, 2017; Palmer et al., 2014). As such, the 2014 KDIGO (Kidney Disease: Improving Global Outcomes) guideline recommendations support the use of statin therapy in stage 3-4 CKD (Wanner and Tonelli, 2014), but not in a dialysed patient given the negative result from the 4D (Wanner et al., 2004) and AURORA (Holdaas et al., 2011) trials. Evolocumab, a pro-protein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibody, has recently been shown to confer ischaemic benefit in a sub-study involving patients with CKD (Charytan et al., 2019). Further research is required to establish the efficacy of PCSK9 monoclonal antibodies in patients with CKD.

Whilst two randomised trials have compared initial optimal medical therapy (OMT) to initial invasive therapy in the general population (Al-Lamee et al., 2018; Boden et al., 2007), the only large randomised trial to-date specific to CKD patients is the recently completed ISCHEMIA-CKD trial (NCT01985360). This trial, which is part of the much larger ISCHEMIA trial, included 777 patients with eGFR < 30ml/min/1.73m² or on dialysis with evidence of moderate-severe ischaemia on functional testing.

These patients were randomised to routine early invasive therapy or OMT. At follow up (median of 2.3 years), invasive therapy did not lead to a reduction in death or MI (36.4 vs. 36.7%, $P = 0.95$) or improvement in symptoms, and was associated with a significant excess in stroke rate. It is important to note, however, that the trial excluded patients with significant left main stenosis, severe left ventricular systolic dysfunction (left ventricular ejection fraction < 35% or New York Heart Association class III-IV heart failure) or recent ACS (acute coronary syndrome). The full findings of this trial as well as long-term follow up are yet to be published.

In conclusion, the assessment and management of stable CAD in CKD patients requires careful consideration of both the associated benefit and risks. Current data support initial non-invasive investigation, OMT and invasive management in selected patients.

5.3 Myocardial injury and potential myocardial therapies

Since the introduction of 5th generation hs-cTn, non-ischaemic troponin elevation above the reference threshold, now termed 'myocardial injury', is commonly seen in patients with CKD; affecting up to 75% of dialysis patient (Gunsolus et al., 2018; Miller-Hodges et al., 2018; Sandoval et al., 2017; Sarkisian et al., 2016; Shah et al., 2018; Tarapan et al., 2019). Numerous studies have suggested that myocardial injury is now the most common cause of troponin elevation and confers a poor prognosis independent of the underlying mechanism of its elevation (Chew et al., 2014; McFalls et al., 2011; Miller-Hodges et al., 2018; Tarapan et al., 2019).

A critical difference between the diagnoses of myocardial injury and acute MI is the disparity in evidence to inform clinical management. While there is rich evidence to guide the management of type 1 MI, there is little evidence to guide the management of patients with myocardial injury (Alpert et al., 2014; Amsterdam et al., 2014; Chuang et al., 2016; Roffi et al., 2016; Sandoval et al., 2017). It is unclear whether the poor prognosis in myocardial injury is solely due to the influence of competing non-cardiac comorbidities (therefore difficult to modify) or secondary to myocardial injury and if so, whether these risks are amendable to current therapies. Further research effort is required to explore potential opportunities for risk-modifying strategies to mitigate the excess cardiac risks in this population.

Currently, there are two ongoing randomised trials investigating the role of invasive coronary assessment in patients with myocardial injury: ACT-2 (The Appropriateness of Coronary investigation in myocardial injury and Type 2 myocardial infarction, ACTRN12618000378224) (Lambrakis et al., 2019) and DEMAND MI (DEtermining the Mechanism of myocardial injury AND role of coronary disease in type 2 Myocardial Infarction, NCT03338504).

Another class of agents that has recently received substantial attention is inhibitors of sodium – glucose cotransporter-2 (SGLT2) including empagliflozin, canagliflozin, and dapagliflozin. Prior to 2019, SGLT2 inhibitors have been shown in multiple large randomised trials to reduce the risk of cardiovascular death, heart failure (HF), hospitalisation and all-cause mortality in patients with type 2 diabetes mellitus (Furtado et al., 2019; Hruska et al., 2011; Jardine et al., 2017; Neal et al., 2017). In November 2019, the DAPA-HF trial reported, for the first time, that the use of dapagliflozin was associated with reduced cardiovascular death (9.6 vs. 11.5%; HR = 0.82, 95% CI 0.69-0.98), HF hospitalisation (10 vs. 13.7%; HR = 0.70; 95% CI 0.59-0.83), improved

Table 3. Areas requiring further research in patients with renal impairment

- Optimal rapid rule-in and rule-out strategies using high-sensitivity troponin
- Better understanding of pathophysiology, investigation, risk stratification and management of patients with acute and chronic myocardial injury
- Anti-platelet and anti-coagulation strategies in acute myocardial infarction
- Selection of patients who may benefit from invasive management and coronary revascularisation in acute myocardial infarction and stable coronary artery disease
- Optimal medical therapy for stable coronary artery diseases
- Role of novel lipid-lowering therapies (e.g. proprotein convertase subtilisin/kexin type 9 monoclonal antibodies)
- Role of potential myocardial therapies (e.g. sodium–glucose co-transporter 2 inhibitors)

physical function and quality of life in non-diabetic patients with systolic heart failure (Kosiborod et al., 2020; McMurray et al., 2019). Of relevance, the trial included patients with an eGFR as low as 30ml/min/1.73m² and subgroup analyses showed that the cardio-protective effect of dapagliflozin was consistent across all group including patients with eGFR between 30–60 ml/min/1.73 m² (Kosiborod et al., 2020; Martinez et al., 2020). Furthermore, canagliflozin has been shown to stabilised the rise in hsTnI for over 2 years in older patients with type 2 diabetes mellitus compared to placebo which showed a gradual increase in troponin levels over the same time period (Januzzi et al., 2017). Given the high prevalence of HF in patients with CKD (House et al., 2019) and evidence showing poorer prognosis with elevated hs-cTn levels (Cardinaels et al., 2016; Januzzi et al., 2019a; Omland et al., 2013), SGLT2 inhibitors may confer clinically meaningful 'myocardial benefit' in patients with CKD; although further research is required.

6. Conclusion and future research

Patients with CKD experience significant excess adverse cardiovascular risk with current evidence to guide practice lacking. Furthermore, their management is complicated by atypical presentation, modified testing accuracy, altered treatment side effect profile as well as a higher likelihood of co-existing comorbidities. The recent FDA approval of hs-cTn in the US will inevitably translate to increased clinical demand for cardiologists, nephrologists, general and emergency physicians. However, this transition offers an exciting opportunity to better identify and subsequently improve outcomes in this growing patient cohort with unmet clinical need. Areas that we propose that require further research in this patient population are listed in Table 3.

Authors' contributions

All authors contributed to manuscript preparation, manuscript review and approval of final manuscript.

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Conflict of interest

All authors have no conflicts of interest to declare pertaining to the current submitted work. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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