

## REVIEW ARTICLE

# Interconnection between cardiovascular, renal and metabolic disorders: A narrative review with a focus on Japan

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## Abstract

Insights from epidemiological, clinical and basic research are illuminating the interplay between metabolic disorders, cardiovascular disease (CVD) and kidney dysfunction, termed cardio-renal-metabolic (CRM) disease. Broadly defined, CRM disease involves multidirectional interactions between metabolic diseases such as type 2 diabetes (T2D), various types of CVD and chronic kidney disease (CKD). T2D confers increased risk for heart failure, which—although well known—has only recently come into focus for treatment, and may differ by ethnicity, whereas atherosclerotic heart disease is a well-established complication of T2D. Many people with T2D also have CKD, with a higher risk in Asians than their Western counterparts. Furthermore, CVD increases the risk of CKD and vice versa, with heart failure, notably, present in approximately half of CKD patients. Molecular mechanisms involved in CRM disease include hyperglycaemia, insulin resistance, hyperactivity of the renin-angiotensin-aldosterone system, production of advanced glycation end-products, oxidative stress, lipotoxicity, endoplasmic reticulum stress, calcium-handling abnormalities, mitochondrial malfunction and deficient energy production, and chronic inflammation. Pathophysiological manifestations of these processes include diabetic cardiomyopathy, vascular endothelial dysfunction, cardiac and renal fibrosis, glomerular hyperfiltration, renal hypoperfusion and venous congestion, reduced exercise tolerance leading to metabolic dysfunction, and calcification of atherosclerotic plaque. Importantly, recognition of the interaction between CRM diseases would enable a more holistic approach to CRM care, rather than isolated treatment of individual conditions, which may improve patient outcomes. Finally, aspects of CRM diseases may differ between Western and East Asian countries such as Japan, a super-ageing country, with potential differences in epidemiology, complications and prognosis that represent an important avenue for future research.

## KEYWORDS

cardiovascular disease, diabetic nephropathy, heart failure, type 2 diabetes

## 1 | INTRODUCTION

In 2021, the International Diabetes Federation estimated that 537 million people aged 20–79 years had diabetes (11% of the global population) and predicted an increase to 783 million by 2045.<sup>1</sup> The Western Pacific region including East Asia has approximately 206 million diabetes patients, with 11 million in Japan alone,<sup>1,2</sup> making it an epicentre of the diabetes pandemic.

The large majority of people with diabetes (approximately 90%) have type 2 diabetes (T2D).<sup>2</sup> It is well established that people with T2D have a high risk for macrovascular and microvascular complications. Heart failure is also a common complication that may be more prevalent than atherosclerotic cardiovascular disease (CVD) in T2D patients.<sup>3–5</sup> However, heart failure has only recently come into focus for therapeutic intervention in people with T2D.<sup>4</sup> In Japan, the number of patients with ischaemic heart disease may have plateaued,<sup>6</sup> whereas the number of patients with heart failure is expected to increase in the future.<sup>7,8</sup> Chronic kidney disease (CKD) is also very common among people with T2D, affecting up to 50% of patients.<sup>9</sup>

Partly as a consequence of these associations, the increasing prevalence of T2D is paralleled by the rising prevalence of heart failure and CKD.<sup>10,11</sup> T2D, heart failure and other types of CVD, and CKD, are closely intertwined at the epidemiological, pathophysiological and molecular levels: so-called cardio-renal-metabolic (CRM) disease.<sup>12</sup> Notably, these relationships seem to not just represent individual diseases being complications of others, but also reflect multidirectional pathophysiological interactions that increase CRM disease risk. However, there may be important differences in the genetics, pathophysiology and epidemiology of CRM disease between Western and East Asian countries such as Japan, which can manifest as differences in complications and prognosis.<sup>13–16</sup> For example, compared with T2D patients of European descent, East Asians tend to have a lower body mass index but a higher incidence of abdominal obesity,<sup>17</sup> earlier  $\beta$ -cell dysfunction, and a higher risk of developing renal complications and strokes.<sup>13</sup> Interestingly, a recent meta-analysis of genome-wide association studies identified 28 novel loci associated with susceptibility to T2D in the Japanese population.<sup>16</sup> Furthermore, Japan is a super-aged society and has the longest life expectancy of any country in the Organisation for Economic Co-operation and Development.<sup>18</sup> Therefore, the profile of CRM disease in Japan may be different from other countries.

This narrative review aims to summarize current knowledge of the epidemiology, molecular mechanisms and pathophysiology of CRM disease, with a focus on Japanese data.

## 2 | METHODS

Articles included in this narrative review were selected based on author expertise, supplemented by searches in PubMed up to 1 May 2022, and citation review of selected primary and review articles. Only articles published in English were considered.

## 3 | CRM DISEASE CONNECTIONS: EPIDEMIOLOGICAL EVIDENCE

Epidemiological studies suggest a multidirectional CRM disease connection. For example, in a cohort study of approximately 1.2 million people with T2D from England, Germany, Japan, the Netherlands, Norway and Sweden that evaluated those initially without concomitant CVD or CKD, 24% of first events were heart failure and 36% were CKD.<sup>19</sup> In the Japanese population in this study, 31% of first events were heart failure and 39% were CKD.<sup>19</sup> In a claims-based study in the United States of approximately 1.2 million people with T2D initiating oral glucose-lowering drugs, 16% were diagnosed with CVD or CKD during follow-up, most commonly heart failure and/or CKD (65%).<sup>20</sup> Furthermore, an analysis of Medicare data from the United States found that the rates of myocardial infarction, heart failure, renal-replacement therapy and death were higher in patients with either T2D or CKD compared with those without either condition, and were highest in those complicated with both T2D and CKD (Figure 1).<sup>21</sup> Notably, in approximately 530 000 individuals with T2D in a US outpatient registry of 271 primary care, cardiology and endocrinology offices, it was uncommon for patients to have isolated T2D without other CRM conditions (atrial fibrillation, cerebrovascular disease, CKD, coronary artery disease, heart failure, hyperlipidaemia, hypertension, hyperuricaemia/gout or peripheral artery disease). Only 6.4% had no other CRM conditions, while 51% had at least three other conditions.<sup>22</sup>

As described in the following sections, there is an abundance of epidemiological evidence on bidirectional interactions between CRM diseases (Figure 2).

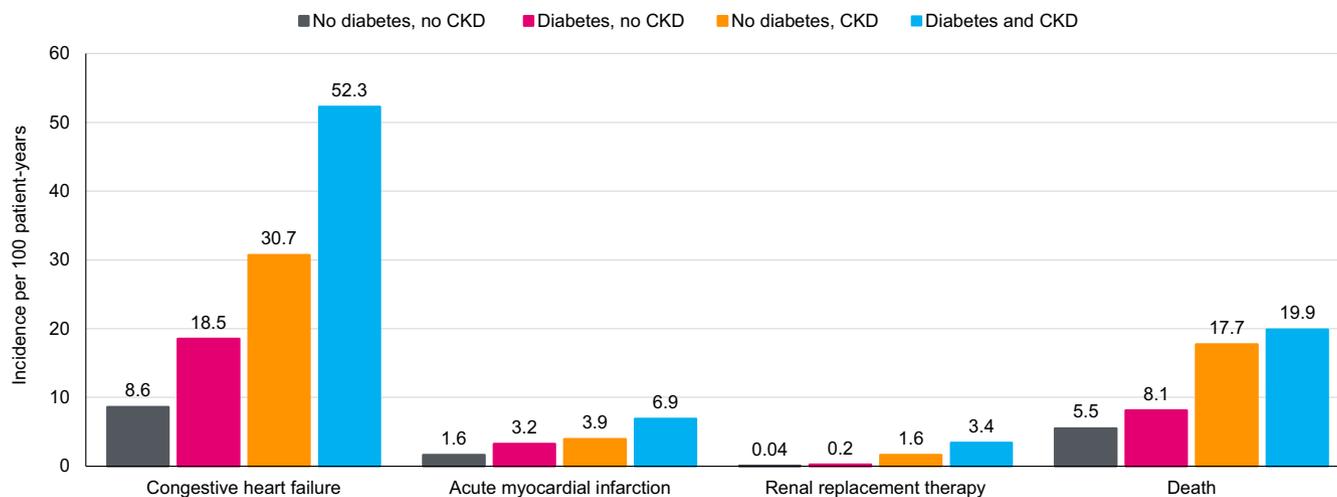
### 3.1 | T2D and CVD

Prospective studies, mainly in Western and other high-income countries, found that the risk of CVD is at least twice as high in people with diabetes compared with those without diabetes.<sup>23</sup> A similar level of excess risk was seen in an analysis of large observational studies in countries in the Asia-Pacific region including Japan<sup>24</sup> and in Japan alone.<sup>25</sup> Important epidemiological studies conducted in Japan are described in the sections below and are summarized in Table 1.

#### 3.1.1 | Heart failure

Until relatively recently, heart failure was an underrecognized complication of T2D.<sup>4</sup> However, it is now clear that heart failure in people with T2D is a significant co-morbidity, especially in ageing populations globally.<sup>4,45–47</sup> Overall, people with T2D are approximately 2–4 times more likely to develop chronic heart failure,<sup>48,49</sup> and there may be differences by race and ethnicity.<sup>5</sup>

Co-morbid heart failure in people with T2D is associated with poor prognosis. For example, a cohort study of Medicare data found that in T2D patients older than 65 years, the coexistence of heart



**FIGURE 1** Rate of cardiorenal complications and mortality with diabetes and chronic kidney disease (CKD). Data from Foley et al. *J Am Soc Nephrol* 2005;16:489-495<sup>21</sup>

failure was associated with 10-fold higher mortality.<sup>50</sup> Conversely, in people with heart failure, the prevalence of T2D is higher than in those without heart failure: up to 4-fold higher in some studies. Overall, the prevalence appears to be approximately 30%-40%, irrespective of heart-failure phenotype (i.e. reduced or preserved ejection fraction), and is even higher in those hospitalized for heart failure.<sup>51-55</sup> The risk of all-cause mortality in people with heart failure may be increased approximately 1.3- to 3.2-fold by co-morbid T2D,<sup>55</sup> while the risk of all-cause hospitalization may be up to 50% higher in heart failure patients with diabetes than in those without the disease.<sup>56-58</sup>

Furthermore, even prediabetes both increases the risk for heart failure<sup>59</sup> and worsens its prognosis.<sup>60</sup>

In Japan, the overall prevalence of heart failure in T2D patients is not firmly established, because of a lack of studies. However, diabetes was associated with a 58% increase in risk for heart failure in individuals in Japan aged 20 to 49 years without established CVD (hazard ratio [HR] 1.58; 95% confidence interval [CI]: 1.41-1.78), based on data for approximately 1.2 million individuals in a national epidemiology database.<sup>35</sup> More information is available on the incidence of diabetes in patients with heart failure in Japan. For example, Japanese registry data for patients hospitalized for heart failure indicated that the prevalence of T2D was 40% to 42% in patients with reduced ejection fraction and 33% to 41% in those with preserved ejection fraction.<sup>31,36</sup>

### 3.1.2 | Ischaemic heart disease

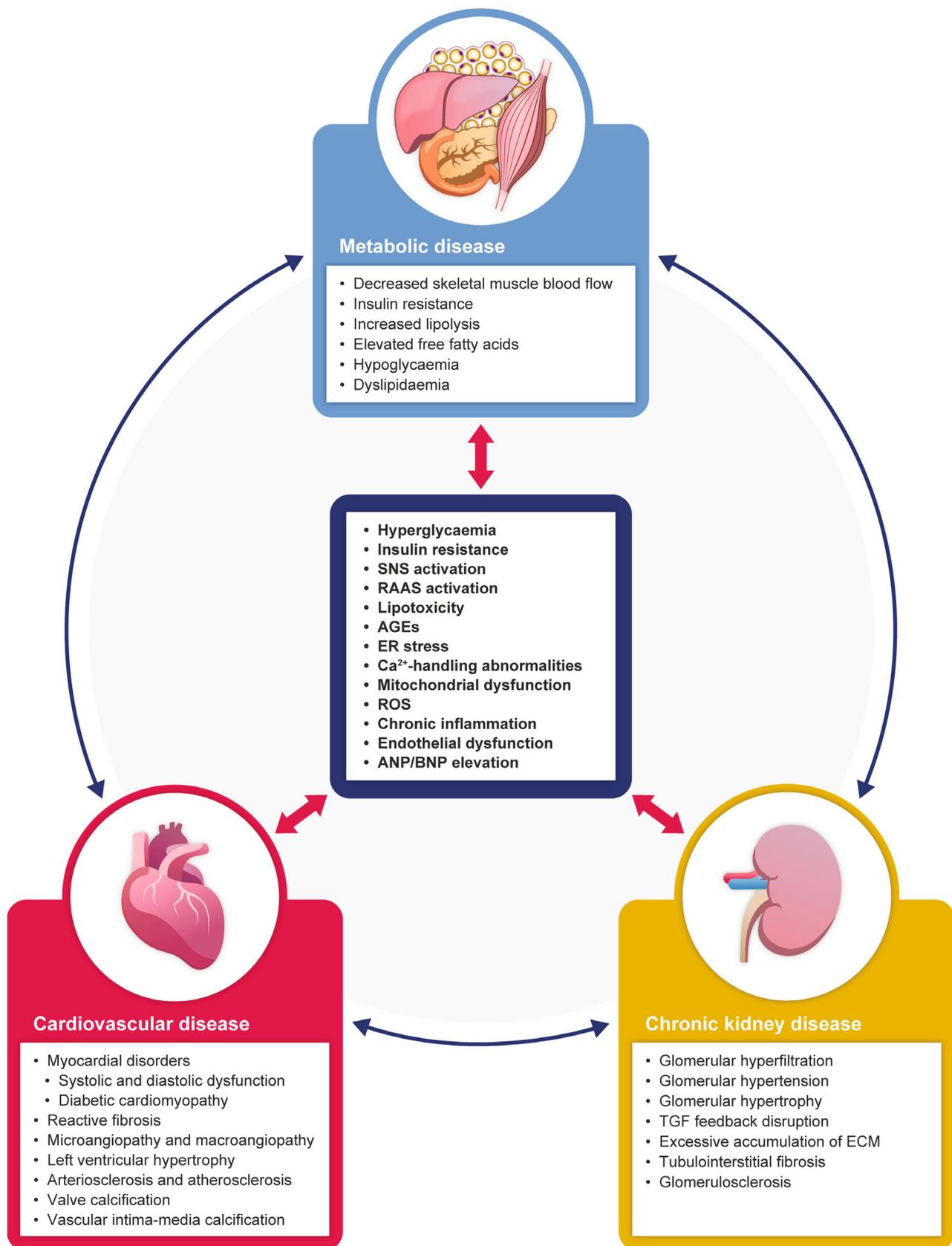
Ischaemic heart disease is a well-established complication of T2D. A meta-analysis of individual patient data for almost 700 000 patients from 102 studies found that T2D patients in high-income countries were approximately twice as likely to develop ischaemic heart disease than non-diabetic patients.<sup>23</sup> Moreover, patients with T2D had a 2.31-fold increased risk for death from coronary heart disease.

Globally, the incidence of coronary artery disease in T2D patients varies across countries;<sup>61</sup> the incidence of myocardial infarction appears to be stable or decreasing in many countries, including the United States and Japan.<sup>6,62,63</sup> Some studies suggest that T2D patients in Asian countries have a lower risk of major coronary events than patients from Europe.<sup>19,64</sup> In cohort studies in Japan, diabetes was estimated to increase the risk of coronary heart disease by approximately 2-fold.<sup>25,29</sup>

### 3.1.3 | Stroke

T2D is also a well-established independent risk factor for stroke, with an approximate 2- to 3-fold increase in risk.<sup>23,65,66</sup> In Asian patients, diabetes is the second-strongest risk factor for stroke after hypertension.<sup>67</sup>

Recent studies have elucidated the epidemiology of stroke in T2D in Japan. In a pooled analysis of eight cohort studies in Japan, diabetes was associated with 40% increased risk for stroke (HR 1.40; 95% CI: 1.05-1.85).<sup>25</sup> Diabetes was also associated with increased risk for stroke in individuals in Japan aged 20 to 49 years without established CVD (HR 1.31; 95% CI: 1.07-1.59) in the study of approximately 1.2 million individuals in a national epidemiology database.<sup>35</sup> In the Japan Public Health Study of approximately 36 000 individuals, the risk of stroke was significantly increased in both men (HR 1.64; 95% CI: 1.21-2.23) and women (HR 2.19; 95% CI: 1.53-2.12) with diabetes compared with those without diabetes.<sup>26</sup> Comparison of the J-DREAMS database study of approximately 10 000 T2D patients in Japan with studies conducted in Europe showed that stroke was more common than myocardial infarction in Japanese patients (7.6% and 2.8% of patients, respectively), but less common than myocardial infarction in European patients (5.0%-9.8% and 7.1%-12.0% of patients, respectively).<sup>37</sup>



**FIGURE 2** Molecular and pathophysiological interplay between cardiovascular disease, chronic kidney disease and metabolic disease. AGEs, advanced glycated end-products; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; ECM, extracellular matrix; ER, endoplasmic reticulum; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; SNS, sympathetic nervous system; TGF, tubuloglomerular feedback

**TABLE 1** Epidemiological studies of cardio-renal-metabolic disease in Japan

Authors (year of publication)	Type of study	Number of subjects	Findings
<i>T2D and CVD</i>			
Shiba et al. (2011) <sup>8</sup>	Prospective, multicentre, cohort study	10 219	22.5% of HF patients had diabetes
Cui et al. (2011) <sup>26</sup>	Prospective, multicentre, cohort study	35 657	Diabetes associated with increased risk of stroke: <ul style="list-style-type: none"> <li>• Men: HR 1.64 (95% CI: 1.21-2.23)</li> <li>• Women: HR 2.19 (95% CI: 1.53-3.12)</li> </ul>
Akao et al. (2013) <sup>27</sup>	Cross-sectional, multicentre, cohort study	3183	23.2% of patients with atrial fibrillation had diabetes
Sato et al. (2013) <sup>28</sup>	Prospective, multicentre, cohort study	4842	33.8% of hospitalized HF patients had diabetes
Kato et al. (2015) <sup>29</sup>	Prospective, multicentre, cohort study	99 584	Diabetes associated with increased risk of death from IHD: <ul style="list-style-type: none"> <li>• Men: HR 2.32 (95% CI: 1.78-3.03)</li> <li>• Women: HR 4.56 (95% CI: 3.17-6.57)</li> </ul>
Takabayashi et al. (2016) <sup>30</sup>	Prospective, multicentre, cohort study	647	31.8% of hospitalized HF patients had diabetes
Hirakawa et al. (2017) <sup>25</sup>	Pooled analysis of 8 cohort studies	38 854	Diabetes associated with an increased risk of death from: <ul style="list-style-type: none"> <li>• CV death: HR 1.62 (95% CI: 1.35-1.94)</li> <li>• CHD: HR 2.13 (95% CI: 1.47-3.09)</li> <li>• Stroke: HR 1.40 (95% CI: 1.05-1.85)</li> </ul>
Yaku et al. (2018) <sup>31</sup>	Prospective, multicentre, cohort study	4056	37% of hospitalized HF patients had diabetes (HFReEF 40%; HFpEF 33%)
Kaku et al. (2020) <sup>32</sup>	Retrospective, multicentre, cohort study	198 861	26.2% of hospitalized HF patients had diabetes
Sato et al. (2020) <sup>33</sup>	Prospective, multicentre, cohort study	4876	39.5% of elderly HF patients had diabetes
Ide et al. (2021) <sup>34</sup>	Retrospective, multicentre, cohort study	13 238	34.2% of hospitalized HF patients had diabetes
Kaneko et al. (2021) <sup>35</sup>	Cross-sectional database study	1 180 062	In individuals aged 20 to 49 years, diabetes was associated with an increased risk for: <ul style="list-style-type: none"> <li>• Myocardial infarction: HR 2.09 (95% CI: 1.61-2.71)</li> <li>• Angina: HR 1.59 (95% CI: 1.42-1.78)</li> <li>• Stroke: HR 1.31 (95% CI: 1.07-1.59)</li> <li>• HF: HR 1.58 (95% CI: 1.41-1.78)</li> <li>• Atrial fibrillation: HR 1.69 (95% CI: 1.35-2.13)</li> </ul>
Seo et al. (2021) <sup>36</sup>	Prospective, single-centre, cohort study	349	43% of hospitalized HF patients had diabetes (HFReEF 42%; HFpEF 41%)
Ohsugi et al. (2021) <sup>37</sup>	Cross-sectional database study	10 151	2.8% of T2D patients had myocardial infarction, while 7.6% had ischaemic stroke
<i>T2D and CKD</i>			
Ohta et al. (2010) <sup>38</sup>	Retrospective, single-centre, cohort study	3575	46.0% of T2D patients had CKD
Iwai et al. (2018) <sup>39</sup>	Prospective, multicentre, cohort study	2484	28.1% of CKD patients had diabetes
Yokoyama et al. (2018) <sup>40</sup>	Cross-sectional, multicentre, cohort study	7251	Prevalence of CKD in T2D patients declined from 32.6% to 22.3% from 2004 to 2014
Nitta et al. (2019) <sup>41</sup>	Cross-sectional, multicentre, cohort study	1088	41.7% of CKD patients had diabetes
Yoshida et al. (2020) <sup>42</sup>	Cross-sectional, multicentre, cohort study	2385	54.0% of T2D patients had CKD
<i>CKD and CVD</i>			
Tanaka et al. (2017) <sup>43</sup>	Prospective, multicentre, cohort study	2966	8.6 HF events per 1000 person-years in CKD patients
Kon et al. (2018) <sup>44</sup>	Cross-sectional, multicentre, cohort study	132 160	HR 2.28 (95% CI: 1.28-4.03) for CV death in elderly patients with eGFR < 45 ml/min/1.73m <sup>2</sup> compared with those with eGFR > 90 ml/min/1.73m <sup>2</sup>
Yaku et al. (2018) <sup>31</sup>	Prospective, multicentre, cohort study	4056	45% of HF patients had CKD
Nitta et al. (2019) <sup>41</sup>	Cross-sectional, multicentre, cohort study	1088	23.4% of CKD patients had left ventricular hypertrophy
Sato et al. (2020) <sup>33</sup>	Prospective, multicentre, cohort study	4876	47.7% of elderly HF patients had CKD
Ide et al. (2021) <sup>34</sup>	Retrospective, multicentre, cohort study	13 238	38.9% of HF patients had CKD

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFReEF, heart failure with reduced ejection fraction; HR, hazard ratio; IHD, ischaemic heart disease; T2D, type 2 diabetes.

### 3.1.4 | Atrial fibrillation

The landmark Framingham Heart Study found an increased risk of atrial fibrillation in patients with diabetes (odds ratio of 1.4 for men, 1.6 for women).<sup>68</sup> Diabetes was also independently associated with atrial fibrillation in a study of individuals in Veterans Health Administration hospitals in the United States (odds ratio 2.13; 95% CI: 2.10-2.16).<sup>69</sup> A meta-analysis of prospective cohort and case-control studies in several Western countries and Japan reported an overall 40% increase in risk for atrial fibrillation in patients with diabetes, compared with those without the disease, although it was only 24% in studies that adjusted for multiple potential confounding factors.<sup>70</sup> Among the approximately 1.2 million Japanese individuals aged 20 to 49 years in the epidemiology database study described above, diabetes was associated with an almost 70% increased risk for atrial fibrillation (HR 1.69; 95% CI: 1.35-2.13).<sup>35</sup>

### 3.2 | T2D and CKD

Globally, it is estimated that up to 50% of T2D patients also have CKD, defined as persistent albuminuria (urinary albumin-to-creatinine ratio  $\geq 30$  mg/g), an estimated glomerular filtration rate (eGFR) persistently less than 60 ml/min/1.73m<sup>2</sup>, or both.<sup>9</sup> In the United States, approximately 25% of patients with T2D also have CKD.<sup>71</sup> In a global study of patients initiating second-line glucose-lowering drugs, approximately 49% also had CKD.<sup>72</sup> Large observational studies in both the United States<sup>73</sup> and Japan<sup>74</sup> found that the mortality risk in people with T2D was increased to a similar degree by albuminuria or reduced eGFR (<60 ml/min/1.73m<sup>2</sup>) and was further doubled in those with both albuminuria and reduced eGFR.

Multiple studies have shown that the risk of CKD is higher in Asians with T2D than their Western counterparts.<sup>13,75</sup> One of the first studies to compare diabetes complications across ethnic groups was the World Health Organization Multinational Study of Vascular Disease in Diabetes, which found a higher incidence of albuminuria in Asians than in Europeans.<sup>76-78</sup> In a cross-sectional study of approximately 32 000 T2D patients from 33 countries, the prevalence of microalbuminuria and macroalbuminuria was 39% and 9.8%, respectively, with Asians having the highest prevalence of albuminuria overall.<sup>79</sup>

A recent systematic review of CKD in Asia found that Japan had the second-highest prevalence in this region (after Singapore). The high prevalence in East Asia was attributed to diabetic nephropathy.<sup>80</sup> Several studies have shown high rates of CKD in T2D patients in Japan. Two studies involving several thousand patients found that approximately 50% had CKD.<sup>38,42</sup> Interestingly, a comparison of two independent cohorts found a declining rate of CKD in Japanese T2D patients between 2004 and 2014 from approximately 40% to 30%.<sup>40</sup>

Unsurprisingly, given the previously described studies showing a high prevalence of CKD in T2D patients, the reverse has also been found: high rates of diabetes in CKD patients in both non-Asian and Asian countries. Among approximately 5200 patients with CKD in the German Chronic Kidney Disease cohort, 50% also had T2D.<sup>81</sup> In

patients with CKD in China, 19.1% of those with eGFR less than 60 ml/min/1.73m<sup>2</sup> had diabetes and 17.3% of those with albuminuria had diabetes.<sup>82</sup> In the KNOWCKD study of approximately 2200 CKD patients in South Korea, 33.7% also had T2D.<sup>83</sup> In recent cohorts of CKD patients in Japan, the prevalence of diabetes was 28% to 42%.<sup>39,41</sup>

### 3.3 | CKD and CVD

CKD is a key co-morbidity in T2D patients, partly because of the important role played by kidney dysfunction in the pathophysiology of CVD, particularly heart failure,<sup>84</sup> as described later in sections 6.1 and 6.2. A meta-analysis of studies involving approximately 1.1 million patients with heart failure found an overall CKD prevalence of 49%, which was higher in patients with acute heart failure (53%) than in those with chronic heart failure (42%).<sup>85</sup>

From the opposite perspective, it is well-established that CVD, including heart failure, is more prevalent among patients with CKD than in the general population, and its prevalence increases as kidney function decreases.<sup>84,86</sup> In the United States, CKD patients had double the risk of heart failure in the ARIC study,<sup>87</sup> while the HOPE study found that the presence of microalbuminuria approximately doubled the risk of hospitalization for heart failure.<sup>88</sup> In the CRIC study in the United States, the rate of heart failure events in CKD patients was 26 per 1000 person-years.<sup>89</sup> In Japan, the large, prospective CKD-JAC cohort study found a rate of heart failure in CKD patients of 8.6 per 1000 person-years.<sup>43</sup>

In the CRIC study, the rate of major adverse cardiovascular events (heart failure, myocardial infarction, stroke) in CKD patients was 38 per 1000 person-years, while myocardial infarction alone was 13 per 1000 person-years.<sup>89</sup> In the CKD-JAC study, the rate of CVD in CKD patients was 22.8 per 1000 person-years, while myocardial infarction occurred in 1.6 per 1000 person-years.<sup>43</sup>

## 4 | T2D IN CRM DISEASE: MECHANISMS AND PATHOPHYSIOLOGY

### 4.1 | Mechanisms for the effect of T2D on the cardiovascular system and kidneys

#### 4.1.1 | Hyperglycaemia and advanced glycation end-products

Hyperglycaemia causes non-enzymatic glycation of lipids and proteins to produce advanced glycation end-products (AGEs).<sup>90</sup> AGEs can directly cause cross-linking of proteins such as collagen and laminin in the extracellular matrix, resulting in vascular stiffening.<sup>90</sup> Furthermore, AGEs bind to the cell surface receptor for AGEs (RAGE), which can promote fibrosis by activating signalling pathways such as nuclear factor- $\kappa$ B (NF- $\kappa$ B), resulting in excessive accumulation of extracellular matrix proteins.<sup>91</sup> These effects are thought to in part underlie the pathophysiology of diabetic cardiomyopathy<sup>92</sup> and diabetic nephropathy.<sup>93</sup>

#### 4.1.2 | Insulin resistance

Impaired insulin metabolic signalling is associated with cardiac fibrosis/stiffness and diastolic dysfunction,<sup>94</sup> and insulin resistance in the heart is considered a major pathophysiological abnormality in diabetic cardiomyopathy. In renal podocytes, defective insulin receptor signalling also leads to a pathology reminiscent of diabetic nephropathy, even with normoglycaemia.<sup>90</sup>

#### 4.1.3 | Lipotoxicity

In T2D, reduced levels of intracellular glucose resulting from insulin resistance, in cells that take up glucose in an insulin-dependent manner, may shift metabolism towards free fatty acid oxidation, a less efficient process. In the diabetic heart, decreased adenosine triphosphate (ATP) production from glucose metabolism may cause compensatory increases in free fatty acid uptake and accumulation of triacylglycerols, which may exceed mitochondrial respiratory capacity, resulting in a build-up of toxic lipid metabolites and mitochondrial dysfunction.<sup>90,92,95</sup> Insulin metabolic signalling is inhibited by certain lipid metabolites, including diacylglycerol and ceramides, which also promotes diabetic cardiomyopathy.<sup>96</sup> Abnormalities in cellular energy production have been documented in both microvascular and macrovascular diabetic complications.<sup>90</sup>

#### 4.1.4 | Hyperactivity of the renin-angiotensin-aldosterone system

Hyperglycaemia is associated with activation of the systemic renin-angiotensin-aldosterone system (RAAS) and increased arterial pressure and vascular resistance.<sup>96</sup> RAAS activation promotes oxidative stress via elevating NADPH oxidase activity and induces insulin resistance both systemically and in the heart via the mammalian target of rapamycin (mTOR)/S6 kinase 1 (S6K1) signalling pathway.<sup>96</sup> In addition, local RAAS signalling in the myocardium also increases inflammation.<sup>96</sup>

#### 4.1.5 | Other mechanisms

Other pathways in T2D that appear to cause cardiovascular and kidney complications include endoplasmic reticulum (ER) stress, abnormal calcium handling, oxidative stress and chronic inflammation.

ER stress—where the capacity of the ER to fold proteins is overwhelmed—appears to play an important role in the pathophysiology of diabetes, and is initiated by several pathways, including the RAAS and AGE-RAGE signalling.<sup>90</sup> ER stress has been implicated in cardiomyocyte apoptosis, atherosclerosis in diabetes and diabetic kidney disease.<sup>90</sup>

Lowered glucose uptake by the heart reduces activity of the Ca<sup>2+</sup> ATPase, increasing intracellular Ca<sup>2+</sup> levels.<sup>96</sup> In addition, excessive

Ca<sup>2+</sup> uptake opens the mitochondrial permeability transition pore, resulting in energy deficiency and oxidative stress.<sup>97</sup> The interaction of aberrant Ca<sup>2+</sup> handling with ER stress and oxidative stress increases autophagy, apoptosis and necrosis, leading to cardiomyocyte death.<sup>92</sup>

Reactive oxygen species (ROS) are produced spontaneously during the formation of AGEs; furthermore, AGE-RAGE signalling also leads to the generation of ROS by NADPH oxidase and mitochondria.<sup>90</sup> Furthermore, in the hyperglycaemic, hyperlipidaemic and inflammatory environment characteristic of diabetes, the activity of mitochondrial enzymes producing ROS is upregulated.<sup>98</sup> In turn, the increased levels of ROS reduce fatty acid oxidation capacity, drive further mitochondrial dysfunction and apoptosis, and lead to lipid accumulation, fibrosis and cardiac dysfunction in patients with diabetes.<sup>96</sup>

In tissues with diabetic complications, various mechanisms mentioned above activate the endothelium, leading to NF-κB activation and increased expression of cytokines and cell adhesion factors, which in turn promotes the recruitment of leukocytes and activation of inflammatory immune cells.<sup>90,92</sup> Renal inflammation may be involved in the pathogenesis of diabetic kidney disease via several pathways, including those mediated by inflammasomes.<sup>99</sup>

### 4.2 | Pathophysiology of T2D in the cardiovascular system

#### 4.2.1 | Diabetic cardiomyopathy and heart failure

Diabetic cardiomyopathy is associated with metabolic disturbances such as impaired insulin metabolic signalling and insulin resistance, increased myocardial free fatty acid uptake and mitochondrial dysfunction.<sup>92,96,100</sup> Together, these pathogenic processes promote fibrosis and diastolic dysfunction.<sup>92,96,100</sup> In later stages, fibrosis and cardiac remodelling become more advanced, associated with impaired insulin signalling, reduced nitric oxide levels, RAAS activation and oxidative stress, which further impairs diastolic and systolic function.<sup>92,96,100</sup>

#### 4.2.2 | Vascular endothelial dysfunction and coronary artery disease

The uptake of glucose by endothelial cells is proportional to plasma glucose concentration. Therefore, during hyperglycaemia, energy production in endothelial cells (which mainly occurs via glycolysis) may become uncontrolled as a result of excess substrate availability, leading to increased production of ROS and, consequently, endothelial dysfunction.<sup>90</sup> Furthermore, vascular repair of the endothelium is impaired because of reduction in endothelial progenitor cells.<sup>90</sup> As described above, various mechanisms in diabetic tissues also result in endothelial activation, disrupting vascular endothelial cells and allowing immune cells such as macrophages and T cells to attach to the vessel wall, eventually resulting in the formation of complex atherosclerotic plaques that can rupture, leading to myocardial infarction and unstable angina.<sup>90</sup>

## 4.3 | Pathophysiology of T2D in the kidneys

### 4.3.1 | Increased glomerular filtration

Haemodynamic changes associated with systemic and intrarenal changes in blood pressure occur early in diabetes and are characterized by glomerular hyperfiltration, which is observed in up to 40% of patients with T2D.<sup>90,101</sup> In early diabetes, the kidneys increase in size as a result of both hyperplasia and hypertrophy; most of this growth occurs in the proximal tubule, resulting in increased reabsorption of glomerular filtrate, which increases GFR via tubuloglomerular feedback.<sup>90</sup> Furthermore, the loss of nephrons as CKD progresses results in hyperfiltration by the remaining nephrons.<sup>102</sup> Hyperfiltration is thought to be the main cause of damage to the glomeruli and anterior glomerular vessels, the filtration components of the kidney.<sup>103</sup>

### 4.3.2 | Structural changes in the glomerulus and tubulointerstitial fibrosis

Glomerular structural changes that occur in diabetic kidney disease include increased thickness of the glomerular basement membrane, fusion of the foot processes, loss of podocytes and expansion of the mesangial matrix.<sup>101</sup> In late stages, glomerulosclerosis develops as a consequence of excessive accumulation of extracellular matrix proteins in the mesangial interstitial space, resulting in fibrosis.<sup>101,104</sup> These changes can lead to initial glomerular hyperfiltration followed by decreased eGFR and/or albuminuria, and eventually kidney failure.<sup>101</sup>

## 5 | CVD IN CRM DISEASE: MECHANISMS AND PATHOPHYSIOLOGY

### 5.1 | Mechanisms for the effect of CVD on renal and metabolic disease

In patients with heart failure, a complex and incompletely understood interplay between several haemodynamic and non-haemodynamic pathways causes kidney dysfunction, including activation of the RAAS, stimulation of the sympathetic nervous system, oxidative stress, inflammation, fibrosis and natriuretic peptides.<sup>105-108</sup> Increased renal vein pressure or decreased renal blood flow activates the RAAS, which worsens kidney function and stimulates the sympathetic nervous system. Suppression of inhibitory cardiovascular reflexes and augmentation of excitatory cardiovascular reflexes also stimulates the sympathetic nervous system, which in turn can activate the RAAS in a vicious cycle. The sympathetic nervous system can damage kidney function through both hypertensive and non-hypertensive mechanisms such as increasing oxidative stress. RAAS activation can also increase oxidative stress, and chronically high aldosterone levels seem to contribute to fibrosis in the myocardium and kidneys. Inflammation

and oxidative stress-related endothelial dysfunction can also induce myocardial and kidney fibrosis. Furthermore, elevated levels of atrial natriuretic peptide or brain natriuretic peptide may also contribute to kidney damage in patients with heart failure.

There is evidence that heart failure can induce insulin resistance and glucose intolerance.<sup>109</sup> Although the exact mechanisms are unclear, myocardial uptake of free fatty acids is normally increased in heart failure, which can cause lipotoxicity and contribute to insulin resistance, as described in section 4.1.

### 5.2 | Pathophysiology of CVD in the kidneys

Renal hypoperfusion because of decreased cardiac output was previously considered the main reason for declining kidney function in cardiorenal syndrome; however, venous congestion is now known to play an important role and may be the main haemodynamic contributor.<sup>85,110-114</sup> Venous congestion also activates endothelial cells via circumferential stretch, leading to increased levels of proinflammatory cytokines such as tumour necrosis factor and interleukin-6 that may worsen cardiac and kidney dysfunction.<sup>115,116</sup>

### 5.3 | Pathophysiology of CVD in metabolism

Atrophy of slow muscle fibres, reduced aerobic metabolic capacity and decreased muscle glycogen content have been documented in the skeletal muscle of patients with heart failure,<sup>117</sup> as has decreased muscle power output,<sup>118</sup> suggesting that reduced exercise tolerance may lead to further metabolic dysfunction.

## 6 | CKD IN CRM DISEASE: MECHANISMS AND PATHOPHYSIOLOGY

### 6.1 | Mechanisms for the effect of CKD on the cardiovascular system and metabolism

Physiological responses to decreasing GFR can elicit activation of compensatory mechanisms including activation of the RAAS, the sympathetic nervous system and the calcium-parathyroid axis (perturbing calcium-phosphate homeostasis), with potentially deleterious cardiovascular effects.<sup>119</sup> Calcium-phosphate imbalance appears to play a role in vascular calcification in CKD patients. In addition to calcification of atherosclerotic plaque in the intimal layer of the artery, CKD is characterized by calcification of the media wall (Mönckeberg-type tunica media calcification), which further stiffens the arterial wall and reduces vascular compliance.<sup>120</sup>

Declining eGFR in CKD is also associated with renal anaemia, chronic inflammation, oxidative stress, increased extracellular fluid and electrolyte abnormalities.<sup>121,122</sup> Insulin resistance occurs early during the course of kidney dysfunction, although the aetiology is unclear.<sup>123</sup>

## 6.2 | Pathophysiology of CKD in the cardiovascular system

As described in sections 4.1.5 and 4.2.2, various pathological mechanisms such as hyperglycaemia, AGEs, RAAS activation, excessive lipid accumulation and oxidative stress can activate the endothelium. Furthermore, as described in section 5.2, venous congestion in CVD can also activate endothelial cells. Endothelial dysfunction triggers atherogenesis,<sup>90</sup> which may be a common link in the pathological interplay between CKD and CVD. Subclinical atherosclerosis may begin at early stages of CKD<sup>124</sup> and may be more prevalent in CKD patients with diabetes than in non-diabetes patients.<sup>125</sup> Calcification may be important in vascular disease in CKD. In haemodialysis patients, mitral annular calcification was found in 74% and aortic valve calcification in 64%, and the risk of death was significantly higher in both groups than in non-calcified valve patients.<sup>126</sup>

## 6.3 | Pathophysiology of CKD in metabolism

CKD-associated insulin resistance is linked to oxidative stress, endothelial dysfunction and inflammation, which can lead to vascular dysfunction and atherosclerosis.<sup>123</sup> CKD also increases the risk of hypoglycaemia via reduced renal clearance of plasma insulin arising from decreased eGFR, reduced hepatic clearance of plasma insulin (thought to be a consequence of toxic uraemic effects on the liver) and impairment of counter-regulatory renal gluconeogenesis.<sup>127</sup> CKD is also associated with dyslipidaemia characterized by increased levels of triglyceride-rich apoB lipoproteins; impaired lipolysis of these lipoproteins appears to be a fundamental underlying reason for this atherogenic lipid profile.<sup>128-130</sup>

## 7 | ETHNIC DIFFERENCES IN CRM DISEASE: POTENTIAL GENETIC CONTRIBUTORS

Interethnic differences in CRM disease may arise partly from genetic variation. A meta-analysis of genome-wide association studies (GWASs) of approximately 900 000 individuals of European ancestry found over 240 loci associated with T2D.<sup>131</sup> A subsequent meta-analysis of GWAS data for approximately 190 000 Japanese people identified 28 novel loci, including those associated with genes related to pancreatic acinar cells and insulin secretion.<sup>16</sup> Furthermore, a structure-function analysis of ethnic-specific variants of another identified locus (PAX4), which encodes a transcription factor involved in pancreatic  $\beta$ -cell development, found decreased expression of a gene involved in pancreatic  $\beta$ -cell survival, suggesting a pathogenic role for these variants.<sup>132</sup> A similar GWAS of a wider East Asian population of over 400 000 individuals found 61 novel loci, including some with lipodystrophy-like traits.<sup>15</sup> These variations may have relevance for clinical differences between ethnic groups, such as the observation that East Asians tend to develop T2D at a lower body mass index than White individuals.<sup>13,14</sup>

Genetic variation may also contribute to interethnic differences in diabetic kidney disease, such as its greater prevalence in Asians than Europeans (section 3.2). In fact, GWASs have found that some loci appear to be associated with diabetic kidney disease in Japanese but not in Europeans.<sup>133,134</sup>

Similarly, genetic variation may play a role in differences in CVD complications of T2D between Asians and non-Asians.<sup>135</sup> Studies have shown various genotypes to be significantly associated with CVD in Asians with T2D, including Japanese, but not in Whites, including alleles encoding proteins involved in glucose and lipid metabolism.<sup>135</sup>

Overall, the contribution of genetic variation to interethnic differences in CRM disease is a nascent field that is an important avenue for future research.

## 8 | CONCLUSIONS

Cardiovascular, renal and metabolic diseases such as T2D interact at the pathophysiological level, resulting in clinical overlap between these conditions. Increased recognition of this overlap by clinicians, particularly the role of metabolic disorders such as T2D, would facilitate a more holistic approach to CRM care, rather than isolated treatment of individual diseases, which may improve patient outcomes.

Mechanisms by which T2D exerts pathophysiological effects on the heart and kidneys include hyperglycaemia, production of AGEs, insulin resistance, hyperactivity of the RAAS, lipotoxicity, ER stress, abnormalities in calcium handling, mitochondrial malfunction and deficits in energy production, oxidative stress and chronic inflammation. Several of these processes, as well as others, also arise in CVD and CKD. The resulting pathophysiological interplay between metabolic disease, the heart and the kidneys forms a vicious cycle of CRM disease (Figure 2).

Compared with T2D patients in Europe and the United States, those in Japan seem to have more heart failure and CKD events, while stroke seems to occur more frequently than ischaemic heart disease complications such as myocardial infarction (in contrast to Western countries). These apparent differences in the epidemiology of CRM disease in Japan compared with other countries may reflect underlying genetic, biochemical and pathophysiological characteristics.

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All the authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE) and were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development and have approved the final version.

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All data discussed in this review are available in the public domain in the cited literature.

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