2-1-2023

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Journal of Diabetes and Its Complications 37 (2023) 108389

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: www.elsevier.com/locate/jdiacomp

Early intervention and intensive management of patients with diabetes, cardiorenal, and metabolic diseases

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ARTICLE INFO

Keywords:
Diabetes
Cardiovascular disease
Obesity
Heart failure
Chronic kidney disease
NAFLD

ABSTRACT

Increasing rates of obesity and diabetes have driven corresponding increases in related cardiorenal and metabolic diseases. In many patients, these conditions occur together, further increasing morbidity and mortality risks to the individual. Yet all too often, the risk factors for these disorders are not addressed promptly in clinical practice, leading to irreversible pathologic progression. To address this gap, we convened a Task Force of experts in cardiology, nephrology, endocrinology, and primary care to develop recommendations for early identification and intervention in obesity, diabetes, and other cardiorenal and metabolic diseases. The recommendations include screening and diagnosis, early interventions with lifestyle, and when and how to implement medical therapies. These recommendations are organized into primary and secondary prevention along the continuum from obesity through the metabolic syndrome, prediabetes, diabetes, hypertension, dyslipidemia, nonalcoholic fatty liver disease (NAFLD), atherosclerotic cardiovascular disease (ASCVD) and atrial fibrillation, chronic kidney disease (CKD), and heart failure (HF). The goal of early and intensive intervention is primary prevention of comorbidities or secondary prevention to decrease further worsening of disease and reduce morbidity and mortality. These efforts will reduce clinical inertia and may improve patients' well-being and adherence.

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https://doi.org/10.1016/j.jdiacomp.2022.108389
Received 15 November 2022; Received in revised form 22 December 2022; Accepted 23 December 2022
Available online 3 January 2023

1. Preamble

Cardiorenal and metabolic comorbidities are common in most people with diabetes and obesity.[1–6] The rising rate of obesity has driven increases in related conditions, including the metabolic syndrome, atherogenic dyslipidemia, prediabetes, diabetes, nonalcoholic fatty liver disease (NAFLD), atherosclerotic cardiovascular disease (ASCVD) and atrial fibrillation, chronic kidney disease (CKD), and heart failure (HF). These conditions frequently cluster together in the same patient, exacerbating the risk of morbidity and mortality, and are also associated with cognitive dysfunction/dementia, pulmonary diseases, cancers, gastrointestinal diseases, immune system abnormalities, and inflammatory disorders.[4–8] In clinical practice, these disorders are often identified and treated late, leading to irreversible advanced pathology.

To reduce delays in diagnosis and treatment of cardiorenal and metabolic disorders to prevent overt manifestations, it would seem reasonable to identify and treat the disease process earlier. Many patients with obesity, metabolic syndrome, and prediabetes have multiple risk factors that help identify who should be managed early and intensively to prevent disease progression. Such an approach is well established in diseases like breast, colon, and other cancers, with wide professional and public acceptance. Yet over the past 20 years, despite increases in effective therapies, cardiometabolic health in the overall population has worsened. Only 6.8 % of adults in the US meet all targets for risk management, with significant disparities by race and ethnicity.[9] Among those with diabetes, only 22 % meet well-established targets.[10] Moreover, people with established cardiorenal disease and HF are often treated late, increasing risk of further complications and death.[7]

Of great concern is the impact of obesity and diabetes—with a projected 55 million patients affected in the year 2060 in the US—and the associated increased risk for cardiorenal and other metabolic disorders.[11] The American Diabetes Association (ADA) recently published a consensus statement recommending early screening for and diagnosis of HF in diabetes, recognizing both the frequency and gravity of this combination.[12] Yet despite mounting evidence that early and intensive combination therapy reduces morbidity and mortality, to date, no medical society has published guidelines specifically related to earlier diagnosis and intervention for obesity, diabetes, cardiorenal, and other metabolic diseases, leaving a void in understanding the timing of screening and intensity of early management of these conditions. A recently published expert consensus on comprehensive care of these conditions—the Diabetes, Cardiorenal, and Metabolic (DCRM) Multispecialty Practice Recommendations—also does not define the timing of early identification and intervention.[7]

To address this gap, we convened a volunteer Task Force including cardiologists, nephrologists, endocrinologists, and primary care physicians—all recognized leaders in their specialties—to develop this set of recommendations, leading the way for the timing of early diagnosis and intensive management in the primary and secondary prevention of comorbidities in patients with metabolic syndrome. These recommendations complement the DCRM Multispecialty Practice Recommendations and other developing comprehensive guidelines in this therapeutic space.[7]

The Task Force recommendations are organized into primary and secondary prevention along the continuum from obesity through diabetes and its eventual comorbidities. Early intervention in obesity may prevent or reduce the development of hypertension, diabetes, dyslipidemia, CKD, atrial fibrillation, and HF. Similarly, early intervention with combination therapy addressing dyslipidemia, dysglycemia, and hypertension may reduce the risks of NAFLD, ASCVD, atrial fibrillation, CKD, and HF. Early intensive and comprehensive therapy with lifestyle changes and multiple medications in CKD, ASCVD, and HF may provide secondary prevention of the next event and reduce further morbidity and mortality. Hence, the goal of early, intensive intervention is primary prevention of comorbidities, and in those with already established disease, early comprehensive intervention should slow progression of disease, reducing more events and mortality.

2. General principles of early intervention

2.1. Early recognition and diagnosis

Broadly, diagnosis and management of each condition discussed herein should be initiated immediately upon first recognition of its onset—often before it meets criteria for diagnosis of a downstream complication. Over 70 % of the US population is overweight or obese;[13] as such it makes sense for clinicians to screen most adult patients early for metabolic conditions. Obesity and hypertension are relatively simple to identify early through physical examinations. The diagnosis of metabolic syndrome, prediabetes, diabetes, lipid disorders, and CKD is based on widely available laboratory studies (Table 1). The recognition of the risks for HF, ASCVD, and fatty liver disease often requires biomarkers along with imaging (Table 2). These tests have become increasingly available and are generally inexpensive. By utilizing them early, it would be expected that recent increases in ASCVD, CKD, and HF would be reduced, saving significant health care costs and, most importantly, improving patients' quality of life and longevity.

2.2. Lifestyle therapy, patient education, and use of technology

Lifestyle therapy is the foundation of *early* intervention in all

Table 1
Diagnostic criteria for cardiorenal and metabolic diseases.

Disease	Diagnosis
Obesity	BMI ≥30 kg/m^2 (≥27 kg/m^2 in East/SE Asian)
Metabolic syndrome	≥3 of the following: • WC >88 cm/35 in (female) or 102 cm/40 in (male) • TG >150 mg/dL • HDL-C <40 mg/dL (male) or <50 mg/dL (female) • FPG ≥100 mg/dL • BP >130/85 mm Hg
Prediabetes	FPG 100–125 mg/dL 75-g, 2-h OGTT 141–199 mg/dL A1C 5.7 %–6.4 %
Diabetes	FPG ≥126 mg/dL 75-g, 2-h OGTT ≥200 mg/dL Random glucose ≥200 mg/dL + symptoms[a] A1C ≥6.5 %
Hypertension	BP >140/90 mm Hg
Lipid abnormalities	LDL-C >100 mg/dL TG ≥150 mg/dL HDL-C <40 mg/dL (m) or < 50 mg/dL (f) Non-HDL-C >130 mg/dL Lp(a) ≥30 mg/dL or ≥75 nmol/L
Fatty liver/NASH	Increased hepatic fat content on US, CT, Fibroscan, or MRI Positive biomarkers (FIB-4)
ASCVD	ASCVD per established criteria (MI, CVA, PVD, CAC >300)
CKD	eGFR <90 mL/min/1.73 m^2 UACR ≥30 mg/g
HF	HFpEF: LVEF ≥50 % HFmrEF: LVEF 41–49 % HFrEF: LVEF ≤40 %

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CAC, coronary artery calcium; CKD, chronic kidney disease; CT, computed tomography; CVA, cerebrovascular accident (i.e., stroke); eGFR, estimated glomerular filtration rate; FIB-4, fibrosis 4 calculation; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRI, magnetic resonance imaging; NASH, nonalcoholic steatohepatitis; OGTT, oral glucose tolerance test; PVD, peripheral vascular disease; SE, Southeast; TG, triglyceride; UACR, urine albumin-creatinine ratio; US, ultrasound.

[a] Increased thirst, hunger, or urination or diabetes complication (retinopathy, neuropathy, CKD).

metabolic conditions for prevention and treatment of obesity, diabetes, hypertension, dyslipidemia, NAFLD, and even cardiovascular, kidney, HF, and related metabolic conditions. Most individuals with overweight and obesity should be encouraged to adhere to a low calorie diet. The Mediterranean and Dietary Approaches to Stop Hypertension (DASH) diets, which involve increased consumption of vegetables, fruit, whole grains, and soluble fiber while avoiding processed foods and refined sugars, have demonstrated efficacy in improving cardiometabolic outcomes.[14,15] A low-carbohydrate diet is generally effective in improving glycemic control and serum triglyceride concentrations in people with overweight/obesity and diabetes.[16] All individuals should also be encouraged to engage in moderate-intensity physical activity for 150–300 min per week, consisting of a combination of aerobic and resistance training.[17]

Clinicians should consider referring patients at risk to dieticians, certified diabetes care and education specialists (CDCES), behavioral psychologists, exercise physiologists, and/or validated weight management programs to enhance implementation of effective weight loss and lifestyle modifications.

Technological innovations will define future management and have already made it easier for patients to monitor their own health. Wearable fitness trackers and validated apps for smart phones and/or computers help patients track diet, physical activity, sleep, and other aspects of lifestyle therapy.[18–20] Ambulatory blood pressure monitors (ABPM) and especially continuous glucose monitors (CGM) are useful tools that promote healthy lifestyle and provide useful information to both clinicians and patients.[21–24]

2.3. Management principle—combatting clinical inertia and improving adherence

Emerging data suggest that the earlier patients achieve therapeutic targets, the better their outcomes, and it is well established that "lower is better" in weight, dyslipidemia, dysglycemia, and hypertension.[25–28] However, traditional approaches to treatment involving sequential therapy, in which agents are added only after one has failed, contribute to clinical inertia and often prevent goal attainment, leading to adverse outcomes. In diabetes, prolonged dysglycemia due to delays in treatment intensification increases the risk of diabetic retinopathy, nephropathy, and neuropathy as well was stroke, HF, and myocardial infarctions (MI) by 51 % to 67 %.[27,28] The most effective strategy to achieve targets promptly and avoid clinical inertia is to use combination therapy early with the highest tolerated doses of medications on top of lifestyle interventions. When patients achieve targets faster, they often feel better and may be more likely to adhere to their treatment regimens.

3. Primary prevention of cardiorenal and metabolic diseases

3.1. Obesity

Obesity (body mass index [BMI] ≥30 kg/m^2; East or Southeast Asian individuals, BMI ≥27.5 kg/m^2) plays a major role in the pathogenesis of diabetes, cardiovascular, renal, and metabolic diseases.[1,6,7] Although some people with obesity are considered to have "metabolically healthy obesity" (MHO), only about 10 % do not have any metabolic syndrome

Table 2
Investigations of traditional cardiovascular risk factors.

Disease	When to investigate	Workup		
		Physical exam, personal and family history, plus:		
		Laboratory	Imaging	Technology
Obesity	BMI ≥30.0 (≥27.5 kg/m^2, East/SE Asian)	A1C, FPG, OGTT[a] Lipid profile[a] eGFR, UACR[a] ALT/AST, FIB-4[a] NT-proBNP[a,b]	Liver US, abdominal CT[a]	CGM, sleep apnea test, ABPM[a]
Metabolic syndrome	Overweight or obesity Dyslipidemia, hypertension Prediabetes, GDM, PCOS	Lipid profile FPG, A1C	Liver US, abdominal CT[a]	ABPM, CGM
Prediabetes	BMI >25 kg/m^2 FPG ≥95 mg/dL, random glucose >140 mg/dL with symptoms[c], A1C ≥5.5% GDM, PCOS	FPG, OGTT, A1C Lipid panel[a] eGFR, UACR[a]	Retinal imaging ECG[a] Liver US, abdominal CT[a]	CGM
Diabetes	Obesity Prediabetes, GDM Metabolic syndrome PCOS Fx Hx T2D CVD	FPG, OGTT, A1C Lipid panel[a] eGFR, UACR[a] NTproBNP, hs-cTnT[a,b]	Retinal imaging ECG, CAC, Echo[a,b] Liver US, abdominal CT[a]	CGM
Hypertension	Every visit	eGFR, UACR[a]	ECG, CXR Consider Echo[a]	Office/home BP monitor, ABPM
Lipid abnormalities	First clinic visit as adult • If normal, check annually in obesity, metabolic syndrome, prediabetes, diabetes First CV event	Lipid panel Consider apoB Lp(a) (once)[d]	ECG CAC, age ≥40 y or 5 y of obesity or diabetes • Carotid US[e]	

Abbreviations: ABPM, ambulatory blood pressure monitor; ALT, alanine aminotransferase; apoB, apolipoprotein B; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; CAC, coronary artery calcium; CGM, continuous glucose monitor; CT, computed tomography; CV, cardiovascular; CVD, cardiovascular disease; CXR, chest X-ray; ECG, electrocardiogram; Echo, echocardiogram; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis 4 calculation; FPG, fasting plasma glucose; Fx Hx, family history; GDM, gestational diabetes mellitus; HF, heart failure; hs-cTnT, high-sensitivity cardiac troponin T; Lp(a), lipoprotein (a); NT-proBNP, N-terminal pro-B-type natriuretic peptide; OGTT, 75-g oral glucose tolerance test; PCOS, polycystic ovary syndrome; T2D, type 2 diabetes; UACR, urine albumin-creatinine ratio; US, ultrasound.

[a] Used to identify or rule out comorbidities.
[b] With HF symptoms (unexplained dyspnea, fatigue, edema).
[c] Symptoms suggestive of diabetes (increased thirst, hunger, or urination) or diabetes complications (e.g., neuropathy).
[d] Test once if family or personal history of premature CVD; many recommend one-time universal screening for all.
[e] If CAC not available.

components. Such individuals may have a lower risk of ASCVD and diabetes than people with metabolically unhealthy obesity, but their risk is still higher than metabolically healthy lean individuals.[29]

The diagnosis of obesity is based on a physical examination of the patient's BMI (Table 1) and should immediately prompt medical evaluation (i.e., history, standard blood tests, etc.) of obesity-related diseases, physical functioning, and quality of life. Although waist circumference provides an index of abdominal obesity and may be a stronger predictor of diabetes and perhaps cardiovascular disease (CVD), measuring waist circumference is difficult to do correctly and in any case unlikely to affect clinical management. Studies may include assessment of oral glucose tolerance, hepatic steatosis and fibrosis, coronary heart disease, and kidney function, along with evaluation of other common complications of obesity, such as sleep disorders and osteoarthritis.[30–32] Persons who are overweight (BMI 25.0–29.9 kg/m^2) with comorbid conditions should be evaluated and managed as if they had obesity.

The goal of obesity management is weight loss, which is best achieved with a strategy including caloric restriction in combination with physical activity (Table 3). Weight reduction of 5 % to 10 % is enough to improve most metabolic abnormalities.[33–35] Lifestyle modification with diet and exercise is the foundation of weight loss. Low-carbohydrate diets may be more effective in improving glycemic control and serum triglycerides than are low-fat diets.[36–39] Increasing physical activity may help prevent further weight gain and also significantly improves insulin sensitivity, blood pressure (BP), lipid parameters, and risk of cardiovascular disease and diabetes, as well as patents' sense of well-being.[40,41]

Using a shared decision–making approach promotes patient acceptance of and adherence to weight loss recommendations.[42] Clinicians should consider referring patients to a dietician, behavioral psychologist, or reputable weight management program. Patient use of validated apps and/or fitness trackers can increase the frequency and duration of physical activity and dietary quality, which may help with weight control.[18–20]

Many if not most patients with obesity will need pharmacologic therapy added to lifestyle therapy if adequate weight loss is not achieved within 3–6 months (Table 3). Once begun, treatment adherence, medication tolerance, and weight loss progress should be evaluated initially monthly, if possible, but no less than every 3 months. Of the agents

Table 3
Management of traditional cardiovascular risks.

Disease		Treatment		
		Initiate lifestyle therapy (see Section 2.2) + medications at diagnosis		
		Monitor ≤8-12 weeks and intensify if goals not met		
	Specific diet	Medications	Procedures	Technology
Obesity	Low calorie	Concomitantly with lifestyle but no later than 3 months after it fails, start LA GLP-1 RA[a] or phentermine/topiramate	Consider endoscopic procedure Bariatric surgery for BMI ≥40 kg/m^2 or ≥35 kg/m^2 with comorbidities	Consider CGM
Metabolic syndrome	Diet per diagnosed condition	Medications as indicated for each diagnosed condition		Consider CGM
Prediabetes	Low carbohydrate	1. GLP-1 RA or tirzepatide 2. Consider TZD, metformin, acarbose		Consider CGM
Diabetes	Low carbohydrate	Combination therapy as needed to: Prevent CV event LA GLP-1 RA or SGLT2i for ASCVD prevention SGLT2i for HF or CKD prevention Manage glucose (consider choice per hierarchy) GLP-1 RA SGLT2i Tirzepatide (if not on GLP-1 RA) Metformin TZD DPP4i Insulin SU	Metabolic surgery or devices as individually appropriate	SMBG, CGM CSII, smart pens
Hypertension	Low sodium Reduce or avoid alcohol	RAASi, CCB, diuretic, BB, MRA If older age or African ancestry, consider CCB, BB, diuretic and if RAASi is prescribed, high dose Combination therapy if BP if ≥20/10 from goal		BP monitor, ABPM
Lipid abnormalities	Lower fat[b] High TG: low carbohydrate, avoid or reduce alcohol	High-intensity statin for: • LDL-C above goal • ASCVD, diabetes, CKD ≥3, high Lp(a), CAC >0, or atherosclerosis on carotid US, independent of LDL-C level • TG ≥150 mg/dL LDL-C ≥50% above goal: initial combination therapy, statin with PCSK9i and/or ezetimibe and/or BA TG >135 mg/dL in ASCVD or diabetes with ≥2 RF: statin + IPE TG >500 mg/dL: statin + fenofibrate and/or OM3-FA		

Abbreviations: ABPM, ambulatory blood pressure monitor; ASCVD, atherosclerotic cardiovascular disease; BA, bempedoic acid; BB, beta blocker; BMI, body mass index; BP, blood pressure; CAC, coronary artery calcium; CCB, calcium channel blocker; CGM, continuous glucose monitor; CKD, chronic kidney disease; CSII, continuous subcutaneous insulin infusion; CV, cardiovascular; DPP4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration ratio; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; IPE, icosapent ethyl; LA, long-acting; LDL-C, low-density lipoprotein cholesterol; MRA, mineralocorticoid receptor agonist; OM3-FA, prescription strength omega-3 fatty acid; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; RAASi, angiotensin-aldosterone system inhibitor; RF, risk factor; SGLT2i; sodium glucose cotransporter 2 inhibitor; SMBG, self-monitored blood glucose meter; T2D, type 2 diabetes; TG, triglyceride; TZD, thiazolidinedione; UACR, urine albumin-creatinine ratio; US, ultrasound.

[a] Indicated for obesity.

[b] Monounsaturated fats preferred for high TG.

currently approved for long-term weight loss, the high-dose glucagon-like peptide 1 receptor agonist (GLP-1 RA) semaglutide once weekly 2.4 mg injection is the most potent available agent, with an average weight loss of 15 %. Approximately 30 % of patients lost >20 % of body weight.[43] If price, tolerability, or injection with the GLP-1 RA is a deterrent, the oral fixed-dose combination of phentermine-topiramate also offers significant weight reductions of 10–12 %.[44] Tirzepatide is a dual glucose-dependent insulinotropic polypeptide (GIP)–GLP-1 RA approved for treatment of type 2 diabetes (T2D). Although not yet approved for obesity management, a once weekly 15 mg injection of tirzepatide reduced mean weight by up to 22 % in a recently completed phase 3 trial for weight loss in people with obesity but without diabetes, approaching the weight loss of bariatric surgery.[45] Both semaglutide and tirzepatide also improved fatty liver disease, reduced progression to diabetes, and markedly improved glycemic control in people with diabetes, and in some patients, these agents even normalized blood glucose.[46–48]

People without access to medical therapy may choose endoscopic therapy with sleeve gastroplasty or an intragastric balloon, which achieves a 13 % to 15 % weight loss.[49,50] Intragastric balloons need to be removed after 6 months. Bariatric surgery should be considered for patients with BMI ≥40 kg/m^2 who are unable to achieve the desired weight loss or those who have a BMI ≥35 kg/m^2 and at least one obesity-related comorbidity (e.g., T2D, hypertension, sleep apnea, NAFLD, osteoarthritis, and especially heart disease).[30–32,51]

3.2. Metabolic syndrome

The metabolic syndrome is defined by the presence of at least 3 of the following conditions: waist circumference >40 in (102 cm) for men, >35 in (88 cm) for women; triglycerides ≥150 mg/dL; high-density lipoprotein cholesterol (HDL-C) <40 mg/dL in men, <50 mg/dL in women; BP >130/85 mm Hg; or fasting plasma glucose (FPG) ≥100 mg/dL (Table 1). The metabolic syndrome represents extreme risk for the development of T2D and ASCVD and requires early intervention to prevent its complications. Dysglycemia—which defines prediabetes—although a component of the metabolic syndrome, is on the continuum to diabetes and will be addressed separately.

Insulin resistance underlies all of the defects that define the metabolic syndrome, affecting glucose metabolism in muscle, liver, and fat, as well as other associated conditions.[52] These include hyperinsulinemia, prediabetes and diabetes, hypertension, inflammation, increased plasminogen activator inhibitor 1 (PAI-1), lipotoxicity, endothelial dysfunction, NAFLD and nonalcoholic steatohepatitis (NASH), polycystic ovary syndrome (PCOS), and ASCVD.[53–56] Elevated uric acid, which is associated with insulin resistance and common in patients with obesity, the metabolic syndrome, hypertension, CKD, and ASCVD, may be predictive of both CKD and ASCVD events.[57] Although directly targeting uric acid alone has not reduced events in trials to date, uric acid reduction is considered one of the mechanisms underlying the efficacy of SGLT2 inhibitors.[58]

Currently, no medications are approved to treat the metabolic syndrome itself, although each individual component should be treated with appropriate therapies (Table 3). The large majority of people with metabolic syndrome have obesity and should be treated with weight loss modalities as described in Section 3.1. Due to their high ASCVD risk, patients with the metabolic syndrome and elevated triglycerides should be treated with a statin to reduce low-density lipoprotein cholesterol (LDL-C) (Section 3.6). For those with elevated BP (Section 3.5), antihypertensive therapy should include a renin angiotensin-aldosterone system inhibitor (RAASi; either an angiotensin-converting enzyme inhibitor [ACEi] or angiotensin receptor blocker [ARB]). If the patient has elevated glucose—hence, prediabetes—follow management as described in Section 3.3.

There is greater urgency and utility to intervene early and intensively in people with the metabolic syndrome, as compared with those with obesity without the syndrome, due to their higher risk for comorbidities. Because the long-acting (LA) GLP-1 RAs (liraglutide, semaglutide, and dulaglutide) and tirzepatide reduce weight, ASCVD risk, fatty liver, and progression to T2D, these agents should be considered for patients with metabolic syndrome.[43,59–61] Metformin is frequently recommended for women with PCOS.[62] Pioglitazone increases insulin sensitivity; delays progression to T2D in those with prediabetes (Section 3.3); reduces triglycerides, albuminuria, markers of inflammation, and fatty liver; and reduces risk of strokes and MI in people with metabolic syndrome, especially those with prediabetes (Section 3.3).[63–65]

3.3. Prediabetes

Individuals with prediabetes generally have metabolic comorbidities similar to those seen in T2D and as such are at increased risk for ASCVD, HF, CKD, and microvascular complications (specifically retinopathy), in addition to their risk of developing T2D.[66–72]

Early treatment of prediabetes may halt progression to diabetes and can even promote reversion to normoglycemia.[73] Thus, the Task Force considers the benefits shown in diabetes prevention studies involving patients with prediabetes to result from *early treatment* of subclinical T2D.[33,65,74] In future, high-throughput metabolomics may be useful for assessment of the risk of developing T2D in patients with prediabetes, once such tests have become more widely available and cost-effective.[75]

Screening for prediabetes should be conducted in all patients who are overweight or who have obesity or components of the metabolic syndrome (Table 2), including children and young adults. The potential benefit in preventing progression to T2D in this vulnerable group outweighs any theoretical risk. During a routine wellness visit, a FPG ≥100 (some experts say even FPG ≥95 mg/dL), a random glucose >140 mg/dL with diabetes symptoms, or A1C ≥ 5.5 % should prompt immediate lifestyle modification.

Upon diagnosis, patients with prediabetes should be screened for retinopathy, nephropathy (see Section 4.3), and neuropathy along with ASCVD risk factors (Sections 3.5 and 3.6). Patients with multiple ASCVD risk factors should be screened for CVD, including ASCVD (Section 4.2) and HF (Section 4.4). Assessment of vascular and endothelial function by arterial applanation tonometry and flow-mediated dilation may be considered.[72] Blood pressure and lipids goals should be similar to those with frank diabetes, including statin therapy for many, if not most, of these patients.[66,76,77] Weight loss through lifestyle intervention is key, similar to the approaches for obesity and metabolic syndrome management. Weight loss of at least 5 % to 10 % may halt if not reverse progression of hyperglycemia and positively affect BP and lipids.[33,35,78,79] Patients should be referred to a CDCES for education on lifestyle management and possibly even CGM.

Currently, no medications are indicated by the FDA for the treatment of prediabetes. However, based on the Diabetes Prevention Program (DPP) results, the ADA recommends lifestyle and metformin. The American Association of Clinical Endocrinologists (AACE) and the International Diabetes Federation (IDF) also recommend pioglitazone and GLP-1 RAs (Table 3). The efficacy of GLP-1 RAs in preventing T2D in people with prediabetes was confirmed in the STEP trial.[43,80] Similarly, tirzepatide in the SURMOUNT trial delayed or prevented progression to T2D and even promoted reversion to normoglycemia.[45]

3.4. Diabetes

Diabetes carries at least 2 to 4 times the risk of MI, stroke, HF, and peripheral arterial disease (PAD) and is the leading cause of CKD.[81,82] In recent years, because of the results of several cardiovascular outcome trials with GLP-1 RAs and sodium glucose cotransporter 2 inhibitors (SGLT2is), the approach to management of diabetes has changed. People with diabetes and established ASCVD or ASCVD risk factors should immediately, upon diagnosis or first encounter, be treated to prevent the next event. In these patients, SGLT2is and LA GLP-1 RAs with proven

efficacy should be prescribed to prevent major adverse cardiovascular events (MACE; cardiovascular death, nonfatal myocardial infarction, and stroke). SGLT2i also have a unique impact on HF and CKD. LA GLP-1 RAs have been shown to prevent strokes and may benefit CKD.[7,68,81,83] The benefits of SGLT2is and GLP-1 RAs proven in clinical trials are independent of glycemic levels, goals, and background glucose-lowering therapy. In fact, several SGLT2is are now indicated for HF and/or CKD in people without diabetes. However, it is imperative to continue managing traditional cardiovascular risks, i.e., dyslipidemia, hypertension, and dysglycemia, to more broadly reduce the risk of complications. Most, if not all, of these patients should be on a statin with a goal LDL-C < 70 mg/dL (Section 3.6) and a goal BP of <130/80 mm Hg, primarily achieved with an ACEi or ARB (Section 3.5). Although somewhat less accepted, early intensive management of hyperglycemia is also key to reducing macrovascular risk. The terms *legacy effect* and *metabolic memory* describe well-documented evidence that intensive glycemic control early in the natural history of diabetes reduces the long-term risk of microvascular complications *and* ASCVD events. Intensive treatment of hyperglycemia involves reducing glucose levels to as close to normal as can be safely achieved.[84–87]

Screening for T2D should be conducted in all patients of all ages who are overweight or have obesity (especially with family history of diabetes), components of the metabolic syndrome, or symptoms suggestive of diabetes (Table 2).

At diagnosis of diabetes, patients should be screened for microvascular conditions (retinopathy, neuropathy, and nephropathy [Section 4.3]) and macrovascular risk factors and complications (Sections 3.5, 3.6, 4.2, and 4.4) as well as NAFLD (Section 4.1). The nephropathy screen should include assessment for albuminuria (urine albumin creatinine ratio [UACR] ≥30 mg/g).

Lifestyle intervention should be focused on a lower calorie and lower carbohydrate diet with increased physical activity designed to lower glycemia, and referral to a CDCES is essential for education on diabetes management. CGM and digital apps and devices should be considered early in therapy (Table 2).

On top of lifestyle to achieve successful and durable glycemic control, initial combination therapy should be prescribed to patients diagnosed with T2D (Table 3). Many of these patients—namely, those with established or at high risk for ASCVD, HF, and CKD—should already be taking a LA GLP-1 RA and/or SGLT2i with demonstrated outcomes benefit in those populations. For glucose control, after GLP-1 RA and/or SGLT2i treatment have been started, the addition of metformin should be considered. Many patients in the US and globally will require lower cost medications; metformin, pioglitazone, and sulfonylureas may need to be considered and can still be effective at attaining glycemic goals. There will also be a subset of patients with low endogenous insulin production who will require insulin therapy to reach glycemic goals. Treatment algorithms from the AACE, DCRM, and to some extent the ADA recommend early combination therapy to successfully reach goals in preference to traditional sequential therapy, which often leads to inertia and "treat to failure".[7,66,83] Combination therapy is the most effective approach to A1C lowering and ASCVD risk reduction and may be most effectively delivered when allied health clinicians such as nurse practitioners and physician assistants are empowered to implement guideline-based treatment.[88] The cost of diabetes therapies should be considered globally, with consideration of documented long-term cost savings that come from reduced burden of diabetes complications.[89]

3.5. Hypertension

Hypertension affects approximately half of all adults and most patients with T2D.[6,90] Blood pressure should be checked at every office visit using standardized methods (Table 2).[91] Patients with elevated readings in the office should perform BP monitoring at home, primarily with a BP monitor and occasionally, as needed, with 24-h ABPM. These approaches are important to identify patients with normal blood pressure vs white coat hypertension.

Based on multiple outcome trials, the target BP for the majority of patients with diabetes and cardiorenal risk is <130/80 mm Hg to reduce lifetime ASCVD, HF, and CKD risk.[26,91–93] However, a goal BP of <120/80 mm Hg is recommended for patients with CKD and those at high risk for strokes as well as many older patients.[91–94] Some frail patients at risk for orthostatic hypotension will benefit from a BP of >140/90 mm Hg.[91,92,94] Initial lifestyle therapy should focus on a low-sodium, high-potassium diet such as the DASH diet, combined with physical activity (Table 3). A referral to a dietician is helpful. Additional healthy behaviors such as adequate sleep and stress-reducing activities such as yoga or meditation are important.

Combination therapy should be initiated if the patient's BP is >150/90 mm Hg at diagnosis or >20/10 mm Hg above the BP goal (Table 3). Many patients with diabetes will require 3 medications to reach the goal of <130/80 mm Hg.[7] A RAASi at maximal dose should be prescribed, especially for patients with diabetes or albuminuria, along with a calcium channel blocker (CCB) and a thiazide-type diuretic. In older adults, those of African ancestry, or those with high sympathetic drive, RAASi may be less effective and require high doses. In these populations, diuretics, beta blockers (BBs), and CCBs are generally more effective to lower blood pressure. If 3 drugs are not enough to reach goal, a mineralocorticoid receptor agonist (MRA) should be added early.[91,92,95]

3.6. Lipid abnormalities

A lipid panel should be conducted at the first clinic visit for all adults (age ≥18 years) to establish a baseline and rechecked every 3–5 years thereafter if values are normal and the patient has no ASCVD risk factors (Table 2). Patients with obesity, the metabolic syndrome, or diabetes should have blood lipid levels checked annually. We recommend that all patients should have lipoprotein (a) [Lp(a)] checked at least once, recognizing that some experts would focus only on patients with a personal or family history of premature ASCVD.[96]

All patients with lipid abnormalities should begin lifestyle efforts as described in Section 2.2. Diet modifications and exercise typically affect triglycerides and HDL-C, with limited impact on LDL-C. Reducing saturated fat in the diet, although somewhat controversial, is still recommended by most experts. For very high triglycerides, patients should limit intake of carbohydrates and alcohol.

Statins are the mainstay of therapy for high LDL-C and dyslipidemia. A growing body of data demonstrate that the earlier patients achieve lower goals, the better is the outcome.[25] Therefore, high-intensity statins should be used as first-line therapy for most patients with diabetes, cardiorenal, and metabolic diseases (Table 3). The LDL-C target should be <100 mg/dL for otherwise healthy patients, <70 mg/dL for patients at high risk of ASCVD events, and <55 mg/dL for those with diabetes, CKD, or heterozygous familial hyperlipidemia (HeFH) and established CVD.[7,96–98] Patients whose LDL-C is >50 % from goal will require initial combination therapy (statin plus ezetimibe, bempedoic acid, or a proprotein convertase subtilisin/kexin type 9 inhibitor [PCSK9i]) to reach lower LDL-C targets.

Imaging tests to detect subclinical atherosclerosis should be used to aid management, encourage patient acceptance of intensive therapy, and improve treatment adherence. Imaging should be conducted at age 40 years if there are no other risk factors or 5 years after the diagnosis of obesity, metabolic syndrome, or diabetes.

For those with triglycerides 135–499 mg/dL who also have had an ASCVD event or have diabetes with ASCVD risk, it is reasonable to consider the omega-3 fatty acid (OM-3FA) icosapent ethyl (IPE) in addition to statin therapy (Table 3). Although some controversy surrounds the efficacy of this agent,[99] IPE is approved for these patients and recommended by the guidelines of relevant medical societies.[7,100] Patients with severe hypertriglyceridemia (>500 mg/dL), regardless of ASCVD risk status, should receive specific triglyceride-lowering therapy such as fenofibrate or a prescription-grade OM-3FA in addition to a

statin to prevent pancreatitis (Table 3).[7,96,97,101]

4. Prevention of events in people diagnosed with cardiorenal and metabolic diseases

4.1. Fatty liver and NASH

NAFLD is characterized by fatty liver and steatosis in people with overweight or obesity, insulin resistance, metabolic syndrome, prediabetes, and T2D.[2] Early intervention in NAFLD is important to prevent progression to NASH.[102,103] Patients should be screened annually by assessing liver function (e.g., aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) (Table 4).[2,104] However, because NAFLD is often present when liver enzymes are within the normal range, fibrosis 4 calculation (FIB-4) and/or imaging with hepatic ultrasound, abdominal computed tomography (CT) scan, or elastography (Fibroscan) are useful for identifying NAFLD and estimating the risk of NASH.[105,106]

Once other causes of liver disease (e.g., infectious hepatitis, cancer, hemochromatosis, and alcohol or drug-related hepatotoxicity) have been ruled out and NAFLD identified, patients should be encouraged to lose at least 5 % to 10 % of body weight, avoid alcohol, and manage other cardiorenal and metabolic risk factors (Table 5). Medical or surgical weight loss interventions should be considered for patients unable to achieve ≥5 % weight loss (Table 5). There are no medications approved to manage NAFLD or NASH, but pioglitazone and perhaps vitamin E showed limited benefit in these patients.[2,107] GLP-1 RA directly or through weight loss and also SGLT2i therapy have shown reduction of liver fat.[2] NAFLD and NASH are associated with significantly increased cardiovascular risk, suggesting the need for intensive cardiovascular risk reduction.

Table 4
Investigation of cardiorenal and metabolic comorbidities.

Disease	When to investigate	Workup		
		Physical exam, personal and family history, plus:		
		Laboratory	Imaging	Technology
NAFLD	At diagnosis	Liver enzymes FIB-4 eGFR	Hepatic US, Fibroscan, hepatic MRE	
ASCVD	Presents with ASCVD event	Lipid profile, apoB, Lp(a) hs-cTnT, NT-proBNP[a] UACR, eGFR[a]	ECG, CCTA, carotid US, MRI, MRA, Echo, nuclear stress test, ABI, LE doppler[b]	Remote arrhythmia monitoring
CKD	Acute kidney failure Fx Hx CKD African ancestry, obesity, hypertension, prediabetes, T2D	eGFR, UACR Electrolytes, PTH NT-proBNP, hs-cTnT[a]	Renal US ECG, CAC[a]	
HF	HF hospitalization Unexplained dyspnea, edema, fatigue, exercise intolerance	NT-proBNP, BNP, hs-cTnT eGFR, UACR	ECG, Echo, CMR	Remote arrhythmia monitoring

Abbreviations: ABI, ankle brachial index; ALT, alanine aminotransferase; apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; CAC, coronary artery calcium; CCTA, coronary computed tomography angiography; CKD, chronic kidney disease; CMR, cardiac magnetic resonance; CT, computed tomography; ECG, electrocardiogram; Echo, echocardiogram; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis 4 calculation: FIB-4 = (age in years × AST)/(platelet count × sqrt[ALT]); Fx Hx, family history; HF, heart failure; hs-cTnT, high-sensitivity cardiac troponin T; LE, lower extremity; Lp(a), lipoprotein (a); MRA, magnetic resonance angiography; MRE, magnetic resonance enterography; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PTH, parathyroid hormone; T2D, type 2 diabetes; UACR, urinary albumin-creatinine ratio; US, ultrasound.

[a] Used to identify or rule out comorbidities.

[b] If claudication or positive ABI.

4.2. ASCVD

Early intervention in ASCVD involves identification of subclinical atherosclerosis by assessment of disease markers such as coronary artery calcium (CAC) (Table 4). The CAC score is prognostic of future ASCVD risk and can be a useful tool to guide shared decision making around prevention interventions and their intensity.[108–112] Statin therapy should be considered for any CAC score >0 (Table 3) to prevent progression of atherosclerosis. A CAC of ≥300 is considered by many to be an ASCVD risk equivalent. Its management is included in the recommendation for secondary prevention.

Secondary prevention therapy including antiplatelet therapy (i.e., aspirin) should be initiated in addition to intensive LDL-C-lowering treatment (Table 5). Aspirin may be considered for patients with CAC >100. Patients with a recent event or procedure may be considered for dual antiplatelet therapy (DAPT) or rivaroxaban plus aspirin in addition to the LDL-C-lowering treatment.

Patients with T2D may benefit from a LA GLP-1 RA or SGLT2i. Because many patients with ASCVD are also at risk for HF, combination therapy with a GLP-1 RA and an SGLT2i is recommended. SGLT2i may also be considered for prevention and treatment of HF and CKD in patients without diabetes.

People with obesity or diabetes who also have ASCVD and/or HF or cardiomyopathy are at higher risk for atrial fibrillation. They should receive prompt diagnosis and management with heart rate–controlling medications (i.e., BBs) and anti-coagulation with non-vitamin K antagonist oral anticoagulants (NOAC) or antiplatelet therapy to reduce morbidity and mortality (Table 5).[113] SGLT2is may also be used to reduce atrial fibrillation events.

4.3. CKD

CKD is important because it is not only a frequent comorbidity of diabetes and hypertension but is associated with high risk for ASCVD and HF. CKD diagnosis is based on a decreased estimated glomerular filtration rate (eGFR) and/or a UACR ≥30 mg/g (Table 1). Stage ≥3 CKD (CKD ≥3) is defined by an eGFR <60 mL/min/1.73 m^2 and is considered a coronary artery disease equivalent.[7,96] Both eGFR and UACR should be evaluated annually in patients at risk (Table 4), and once CKD is diagnosed, intensive treatment must be initiated and disease progression should be monitored using the same values.[67,114,115] The Kidney Disease: Improving Global Outcomes (KDIGO) heat map shows the different stages of CKD based on eGFR and albuminuria and serves as a useful tool for choosing interventions and educating patients about CKD risks.[116]

Lifestyle therapy should include a low-sodium diet to avoid worsening hypertension and reduce the risk of HF (Table 5). Low protein diets have not generally been proven to be beneficial, but patients should avoid eating a high-protein diet.[114,115]

Medications should be started promptly in people with CKD, including a RAASi (ACEi or ARB) at the maximum-tolerated dose (Table 5).[117] An SGLT2i should be used regardless of the presence of T2D to delay CKD progression and risk of cardiovascular events including HF.[67,114,118–121] An initial decrease in eGFR is expected with both RAASi and SGLT2i; neither medication should be discontinued unless serious acute kidney injury is suspected based on a >30 % decrease in eGFR. Reductions in eGFR associated with SGLT2i generally return to baseline within a few months.[122] The nonsteroidal MRA finerenone should be added in patients with T2D and CKD with persistent albuminuria.[7,123–125] Although not yet indicated for CKD, GLP-1 RAs may be useful to reduce progression of albuminuria in CKD. All of these

Table 5
Management of cardiorenal and metabolic comorbidities.

Disease	Treatment			
	Initiate lifestyle therapy (see Section 2.2) + medications at diagnosis			
	Monitor ≤8-12 weeks and intensify if goals not met			
	Specific diet	Medications	Procedures	Technology
Fatty liver/ NASH	Avoid alcohol Low fat, low carbohydrate	Statin for all Obesity: LA GLP-1 RA[a] T2D: pioglitazone, LA GLP-1 RA, tirzepatide	Consider bariatric surgery	
ASCVD		High-intensity statin, in combination with other lipid-lowering drugs if ≥50% from LDL-C goal T2D: LA GLP-1 RA or SGLT2i T2D + age >40 y: add aspirin 81 mg/day Recent CV event: consider DAPT or aspirin + rivaroxaban Atrial fibrillation: BB + NOAC or antiplatelet		Arrhythmia: remote monitoring
CKD	Low sodium	Max-tolerated RAASi + SGLT2i T2D and albuminuria: may add nonsteroidal MRA T2D or obesity: consider adding LA GLP-1 RA[a]		
HF	Low sodium	Initial combination therapy based on LVEF: • HFrEF—4 pillar regimen: SGLT2i + ARNI (or RAASi if ARNI intolerant) + MRA + BB • HFmrEF: SGLT2i + ARNI or RAASi; consider adding MRA and/or BB • HFpEF: SGLT2i + RAASi; consider ARNI + MRA (up to 55–60%) Include diuretic if congestion present		

Abbreviations: ARNI, angiotensin receptor neprilysin inhibitor (sacubitril/valsartan); ASCVD, atherosclerotic cardiovascular disease; BB, beta blocker; CKD, chronic kidney disease; CV, cardiovascular; DAPT, dual antiplatelet therapy; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LA GLP-1 RA, long-acting glucagon-like peptide 1 receptor agonist; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor agonist; NOAC, non-vitamin K antagonist oral anticoagulant; RAASi, angiotensin-aldosterone system inhibitor; SGLT2i; sodium glucose cotransporter 2 inhibitor; T2D, type 2 diabetes.
[a] Indicated for obesity.

medications will not only improve kidney function but may also improve HF and/or ASCVD and cardiovascular mortality.

4.4. HF

HF is commonly under-recognized and under-treated, in part because symptoms are frequently subtle and may be attributed to other causes, particularly in patients with preserved ejection fraction (HFpEF, with left ventricular ejection fraction [LVEF] ≥50 %), which make up 56 % of the HF population.[12,126–128] Another 31 % of HF patients have HF with reduced ejection fraction (HFrEF; LVEF ≤40 %) and 13 % have mildly reduced ejection fraction (HFmrEF; LVEF 41 % to 49 %).[128]

N-terminal pro-B-type natriuretic peptide (NT-proBNP) or B-type natriuretic peptide (BNP) can be used to identify patients at risk of HF and patients with underlying asymptomatic structural heart disease as well as to stratify those diagnosed with the disease (Table 4).[12,129] Obtaining a baseline level is useful for these biomarkers, and they should be measured annually in patients at high risk for HF, such as those with hypertension, the metabolic syndrome, diabetes, CKD, or ASCVD.[12,129–131] In a similar fashion, high concentrations of high-sensitivity cardiac troponin T (hs-cTnT) are strongly predictive of risk for HF among those with or without diabetes.[132,133] The ADA recently issued a consensus statement recommending yearly measurement of either in an effort to identify presence of unrecognized HF.[12] Among persons with diabetes, when trended over time, both NT-proBNP (or BNP) and hs-cTnT tend to rise ahead of clinical decompensation, affording opportunity for earlier intervention.[132] In such individuals, transthoracic echocardiogram with Doppler flow should be employed to identify cardiac structural abnormalities and assess LVEF.[134]

HF is a progressive condition, and general management includes aggressive treatment of comorbidities with lifestyle and appropriate medications (Table 5). Patients with hypertension and/or low eGFR and/or albuminuria should be prescribed a RAASi, and those with or without T2D should receive a SGLT2i, which is uniquely appropriate for early intervention, showing benefit as early as 4 weeks after starting therapy.[135,136] Patients with hypertension and/or low eGFR and/or albuminuria should be prescribed a RAASi, and those with T2D or CKD should receive a SGLT2i. Both classes are also part of the treatment regimen for HF (Table 5) and should be given to patients with HFpEF. Those with HFrEF or HFmrEF should be treated according to the 4-pillar approach, which includes an angiotensin receptor neprilysin inhibitor (ARNI; i.e., sacubitril/valsartan), a BB, an MRA (finerenone if the patient has T2D and CKD with albuminuria; otherwise spironolactone or eplerenone), and an SGLT2i.[7,137,138] A diuretic should be added if the patient has congestion.[7,137,138] Prompt initiation of this regimen will improve patients' quality of life, which increases acceptance, and can prolong the lifespan by up to 8 years.[139,140]

5. Conclusions

Multiple outcome trials across a wide range of conditions have shown that early intervention reduces adverse outcomes and lengthens lifespan. Yet the majority of US adults remain at high risk from cardiorenal and metabolic diseases despite the availability of many medications with proven positive impacts on outcomes. Failure to significantly reduce risk is largely due to traditional stepwise, sequential management with low-dose medications, which promotes clinical inertia and the inability to reach goals, in turn contributing to increased morbidity and mortality. In contrast, early diagnosis and prompt, intensive intervention, often with initial combination therapy, leads to faster goal attainment and improved outcomes for at-risk patients.

The primary objective of early intervention is to slow or delay disease progression and prevent further events along the continuum of cardiorenal and metabolic diseases extending from obesity through T2D to ASCVD, HF, and CKD, both in primary and secondary prevention. We can reduce if not prevent cardiovascular and kidney events by following guideline-directed medical therapy and utilizing contemporary medications that when used at maximal dosages and, as needed, in combination, enable patients to rapidly reach treatment goals for traditional cardiovascular risk factors. Newer therapies may safely permit achievement of more stringent therapeutic goals than previously possible. These modern approaches include use of high-intensity statins

in combination with PCSK9i, ezetimibe, and/or bempedoic acid or use of LA GLP-1 RAs in combination with SGLT2i, pioglitazone, and/or metformin. Meanwhile, based on new evidence, some agents' uses have expanded beyond traditional risk control and their original indications. For example, the SGLT2is and LA GLP-1 RAs have positive impacts on the heart, brain, liver, and kidney independent of glucose control; IPE reduces cardiovascular events beyond its effects on lipids; and non-steroidal MRA has beneficial effects on the kidney and heart.

Utilizing the full spectrum of available medications will help us prevent disease complications and promote better quality life and longevity. This approach may also benefit society by reducing direct and indirect costs and loss of productivity associated with cardiorenal and metabolic diseases.

CRediT authorship contribution statement

All authors made significant contributions to the conceptualization and design of this consensus document and the interpretation of data cited herein. The manuscript was drafted by Y.H., J.B., G.L.B., R.A.D., G. C.F., J.B.G., G.G., J.L.J., S.K., P.R.K., D.K.M., E.D.M., J.M., R.E.P., M.R. W., E.E.W., and V.A.F. All authors critically reviewed and provided commentary on the consensus recommendations and the manuscript.

Declaration of competing interest

None of the Task Force members received monetary renumeration for their contributions to the creation or writing of this consensus document. See Appendix A for full declarations of competing interests for each author.

Acknowledgments

We thank the members and staff of the Diabetes, Cardiorenal & Metabolism Institute and the Metabolic Endocrine Education Foundation (Tarzana, California) for their support and important contributions to this endeavor. Amanda M. Justice, independent consultant, Brooklyn, NY, provided editorial and medical writing support, which was funded by the Diabetes, Cardiorenal & Metabolism Institute (Tarzana, California).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jdiacomp.2022.108389.

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