KEY CHANGES IN MANAGEMENT OF CARDIOVASCULAR-KIDNEY-METABOLIC (CKM) DISEASE

The following box highlights the major changes for best management of CKM disease from current care. These new recommendations and other minor changes are discussed in detail in each section.

New major changes in the recommended management of CKM disease

- Obesity is now characterised as preclinical obesity or clinical obesity
  - Preclinical obesity – excess adiposity with preserved function of tissues and organs
  - Clinical obesity – excess adiposity impacting function of tissues, organs or wellbeing
- Excess adiposity is defined as:
  - BMI > 40kg/m^2 OR
  - BMI > ethnicity-specific threshold for obesity and ≥ 1 anthropometric criteria OR
  - Two increased anthropometric criteria regardless of BMI
    - Anthropometric criteria include waist:height ratio > 0.5, increased waist circumference, waist:hip ratio > 0.86 in women and > 1 in men, and body fat percentage on DEXA or bioimpedance > 30% for men and > 42% for women.
- New guidance on targeted personalised interventions for weight loss
- New diagnostic HbA1c cut-off for diabetes is ≥ 48 mmol/mol
- New key consensus treatment targets for CKM disease:
  - Systolic blood pressure 120 – 129 mmHg OR lowest reasonably and safely achievable
  - HbA1c < 53 mmol/mol
  - LDL cholesterol < 1.4 mmol/L for secondary prevention OR if high CV risk
  - LDL cholesterol < 1.8 mmol/L if treating when low to moderate CV risk
  - Serum urate < 0.36 mmol/L if gout and < 0.3 mmol/L if tophi
- Treatment of CKM disease should ideally be optimised 1-3 monthly until to target
- New treatment thresholds for blood pressure (BP)
  - BP ≥ 140/90 mmHg → prompt confirmation and treatment in all if appropriate
  - BP 130 – 139/80 – 89 mmHg → confirm & treat if 5 year CV risk ≥ 10% OR ANY of:
    - Known CVD including asymptomatic disease, AF or heart failure
    - Diabetes with any vascular complication
    - Chronic kidney disease (UACR > 3 mg/mmol and/or eGFR < 60 mL/min)
    - Familial hypercholestrolaemia
- Choice of BP lowering agents now primarily based on presence of kidney disease
  - Kidney disease → ACEi or ARB to maximal tolerated dose
    - Add calcium channel blocker (CCB) or thiazide diuretic if BP above target
  - No kidney disease → low dose ACEi or ARB and CCB in combination
- Chronic kidney disease should be now treated irrespective of BP, diabetes or CV risk
  - ACEi or ARB if no concerns over hypotension
  - Empagliflozin irrespective of diabetes and GLP1Ra if HbA1c still above target
- Atorvastatin and rosuvastatin +/- ezetimibe are preferred lipid lowering therapy
- People with CKM disease should have regular assessments to determine whether developed other features of CKM disease and to reduce CV risk:
  - Preclinical obesity → at least 5 yearly assessments
    - At least 3 yearly assessments if high-risk e.g. Māori or Pacific ethnicity
  - Other features of CKM disease → annual assessments
- High CV risk is now defined as a 5 year CV risk ≥ 10% OR any of the following:
  - Previous CV event
  - Established CVD including known asymptomatic coronary or carotid disease
  - Urinary ACR > 30 mg/mmol and/or eGFR < 45 mL/min
  - UACR 3 – 29 mg/mmol and eGFR 45 – 59 mL/min
  - Age > 50 years and UACR > 3 mg/mmol and/or eGFR < 60 mL/min
  - Diabetes with any vascular complication
  - Familial hypercholesterolaemia
- Moderate CV risk is now defined as a 5 year CV risk 5 - <10% and low CV risk if < 5%
- Antiplatelet therapy remains important for secondary prevention but the risks typically outweigh the benefits if diabetes, significant renal disease or > 70 years of age

DEFINTIONS OF CKM DISEASE

- Definitions of CKM disease have been updated to align with international criteria:
    - Obesity is now characterised as preclinical obesity or clinical obesity
        - Preclinical obesity is defined as excess adiposity with preserved function of other tissues and organs.
        - Clinical obesity is defined as excess adiposity impacting the function of tissues, organs and the entire individual including:
            - CKM disease e.g.:
                - Hypertension
                - Type 2 diabetes
                - Dyslipidaemia
                - CV disease including ischaemic heart disease, cerebrovascular disease, peripheral vascular disease, atrial fibrillation and heart failure
                - Chronic kidney disease
                - Metabolic dysfunction-associated steatotic liver disease (MASLD)
                - Gout
                - Obstructive sleep apnoea (OSA)
            - Non-CKM disease e.g.:
                - Joint pain and osteoarthritis
                - Lymphoedema
                - Reduced age-adjusted mobility
                - Raised intracranial hypertension
        - Excess adiposity is defined as:
            - BMI > 40kg/m^2 OR
            - BMI > ethnicity-specific threshold AND one increased anthropometric criteria OR
                - > 35 kg/m^2 in Pacific peoples
                - > 32 kg/m^2 in Māori
                - > 30 kg/m^2 in Europeans
                - > 25 kg/m^2 in Asian Indians
        - Two increased anthropometric criteria regardless of BMI
            - Anthropometric criteria include:
                - Waist:height ratio > 0.5
                - Increased waist circumference
                    - > 88 cm in females and > 102 cm in males of non-Asian Indian ethnicity
                    - Waist circumference > 80 cm in females and > 90 cm in males of Asian Indian ethnicity
                - Waist:hip ratio > 0.86 in women and > 1 in men
                - Body fat percentage by DEXA or bioimpedance > 30% for men and > 42% for women
    - HbA1c diagnostic threshold for diabetes is now ≥ 48 mmol/mol
    - Chronic kidney disease is defined as a persistent UACR > 3 mg/mmol and/or eGFR < 60 mL/min
    - Hypertension is defined as BP ≥ 140/90 mmHg
        - Elevated BP is defined as a BP 130 – 139/80 – 89 mmHg.

CLINICAL ASSESSMENTS IN PEOPLE WITH CKM DISEASE

- People with CKM disease should be assessed annually to determine whether there has been any progression, complications or development of other CKM disease
- Clinical assessments should include at least:

- Smoking status and alcohol intake
- Waist circumference and BMI
- Seated blood pressure (BP) + standing BP if any concerns over postural hypotension
- HbA1c +/- fasting glucose (may be relaxed to 3 yearly if no known diabetes and HbA1c < 42 mmol/mol)
- eGFR and urinary ACR
- Non fasting lipid studies
- Serum urate if history of gout (may need to ask at assessment)
- Epworth sleep score if history suggestive of obstructive sleep apnoea
- PHQ-2 for screening for depression
- DDS2 if known diabetes for screening of diabetes distress
- Foot examination and check of retinal photoscreening if diabetes
- Calculation of 5 year CV risk on PREDICT CV risk calculator at diagnosis of CKM disease and then as required:
    - Low CV risk (5 year CV risk < 5%) → 5 yearly
    - Moderate CV risk (5 year CV risk 5 – <10 %) → yearly
        - May be relaxed to 2 yearly if gout or MASLD alone
    - High CV risk (5 year CV risk ≥ 10%) → no need to repeat as optimise treatment
    - High CV risk includes any of the following irrespective of calculated risk:
        - Previous CV event
        - Established CV disease including known asymptomatic coronary or carotid disease
        - Diabetes with any vascular complication
        - Urinary ACR > 30 mg/mmol
        - eGFR < 45 mL/min
        - UACR 3 – 29 mg/mmol and eGFR 45 – 59 mL/min
        - Age > 50 years and UACR > 3 mg/mmol and/or eGFR < 60 mL/min
        - Familial hypercholesterolaemia

- People with CKM with blood pressure, lipids, urate (if gout) or glucose levels above target should be reviewed at least every 1-3 months with escalation of treatment until targets are reached.

- People with preclinical obesity without CKM disease should be assessed at least 5 yearly to determine whether they have developed other CKM disease and to reduce CV risk. The interval should be reduced to at least 3 yearly if any of the following risk factors:
    - Māori, Pacific, South-East Asian and other non-European ethnicities
    - Socioeconomic deprivation
    - Direct family history of CKM at < 40 years of age
    - Smoker
    - Post transplant
    - History of preeclampsia or gestational diabetes
    - Long term glucocorticoid and/or antipsychotic use
    - Chronic dental and/or peridontal disease
    - Clinical features of insulin resistance e.g. acanthosis nigricans, PCOS etc.

LIFESTYLE MANAGEMENT AND INTERVENTIONS FOR WEIGHT LOSS

- New guidance on major pillars of lifestyle management:
    - Education and support
    - General holistic care
    - Healthy eating
    - Physical activity and movement
    - Healthy sleep

- New guidance for interventions for weight loss including:
    - Introducing medical targets for weight loss and recommendations for personalised supportive care including utilising local programmes and multidisciplinary team
    - Updated pragmatic recommendations for evidence based nutritional strategies for weight loss
    - New guidance on pharmacotherapy for weight loss including unfunded and off-label options::
        - GLP1 receptor agonists including liraglutide, semaglutide and tirzepatide
        - Bupropion ± naltrexone
        - Phentermine ± topiramate
        - Orlistat
    - Bariatric surgery continues to be an important option

MANAGEMENT OF HYPERTENSION AND ELEVATED BLOOD PRESSURE

- New recommended thresholds for treatment of high BP
    - BP ≥ 140/90 mmHg → confirm and treat with lifestyle advice and pharmacotherapy in all if appropriate
    - BP 130 – 139/80 – 89 mmHg → confirm and treat with lifestyle advice and pharmacotherapy if 5 year CV risk ≥ 10% OR ANY of the following:
        - CVD including ischaemic heart disease, cerebrovascular disease, peripheral arterial disease, atrial fibrillation, heart failure and asymptomatic coronary and carotid disease
        - Diabetes with any vascular complication
        - Chronic kidney disease - eGFR < 60 mL/min and/or UACR > 3 mg/mmol
        - Familial hypercholesterolaemia
    - BP 130 – 139/80 – 89 mmHg and 5 year CV risk 5 - < 10% → lifestyle advice and treat underlying condition and consider pharmacotherapy if ANY of the following:
        - Gout or auto-immune inflammatory disease
        - MASLD
        - OSA
        - Severe mental illness particularly with antipsychotic use
        - Previous gestational diabetes and/or preeclampsia
        - Direct family history of CVD < 40 years of age
        - Cardiac calcium score ≥ 100
    - BP 130 – 139/80 – 89 mmHg and 5 year CV risk < 5% → lifestyle advice alone

- New primary treatment target is systolic BP of 120 – 129 mmHg
    - < 120 mmHg is no concern if well tolerated and likely preferable if young or heart failure
    - Target should be relaxed to lowest reasonable and safely achievable if:
        - Frailty and/or limited life expectancy
        - Age ≥ 85 years
        - Symptomatic postural hypotension
        - Intolerant of BP lowering medication
    - Diastolic BP is no longer a primary target

- First line BP lowering agents are ACE inhibitors (ACEi) or angiotensin receptor blockers (ARB), calcium channel blockers (CCB) or thiazide diuretics (TD). Choice of agents is primarily dependent if chronic kidney disease (UACR > 3 mg/mmol and/or eGFR < 60 mL/min) is present:
    - Evidence of kidney disease → ACEi or ARB and increase to maximal tolerated dose
        - Add CCB or TD if BP is above target
        - Add other class (e.g. TD if on CCB) if BP still above target
    - No kidney disease → low dose CCB and ACEi or ARB in combination
        - Increase doses if BP above target
        - Add TD if BP remains above target

- Cardioselective β blockers may be added at any time if ischaemic heart disease or heart failure, or for rate control
- Entresto (sacubiltril/valsartan) is preferred renin angiotensin system inhibitor in heart failure

- BP should be measured 1 – 3 monthly until to target
  - Home or out of clinic BP monitoring ideal if possible
  - Combine with standing BP if risk of postural hypotension

MANAGEMENT OF GLUCOSE LEVELS IN TYPE 2 DIABETES

- No change to current management algorithm of type 2 diabetes except for emphasising the consideration of pioglitazone (due to its efficacy in primary and secondary prevention of CV events) and acarbose (due to data in aiding weight loss) before sulfonylureas and insulin.

MANAGEMENT OF DYSLIPIDAEMIA

- Lipid targets now differ from 2018 Cardiovascular Management Guidelines
  - Lipid lowering therapy should be started aiming for LDLc < 1.4 mmol/L if any of the below:
    - Previous CV event or established CV disease
    - 5 year CV risk ≥ 10% or any of the following irrespective of calculated risk:
      - Diabetes with any vascular complication
      - Urinary ACR > 30 mg/mmol
      - eGFR < 45 mL/min
      - UACR 3 – 29 mg/mmol and eGFR 45 – 59 mL/min
      - Age > 50 years and UACR > 3 mg/mmol and/or eGFR < 60 mL/min
      - Familial hypercholesterolaemia
  - Lipid lowering therapy is strongly recommended if moderate CV risk (5 year CV risk 5 - < 10%) aiming for LDLc < 1.8 mmol/L, particularly if any of the following risk factors:
    - Direct family history of CVD < 40 years of age
    - Onset of cardiokidney metabolic disease at < 40 years of age
    - Severe mental illness particularly with antipsychotic use
    - Cardiac calcium score ≥ 100
    - Gout and/or autoimmune inflammatory disease
    - Metabolic dysfunction-associated steatotic liver disease
  - Lipid lowering therapy should be still considered if low CV risk (5 year CV risk < 5%) if any risk factors above, particularly if 5 year CV risk ≥ 3% and/or LDLc > 4 mmol/L, but is largely driven by patient preference.

- Atorvastatin and rosuvastatin are first line lipid lowering agents and should be titrated every 1-3 months based on non-fasting LDLc measurements until LDLc to target
  - Add ezetimibe if LDLc above target on maximal tolerate dose of statin
  - Consider alirocumab or inclisiran if LDLc still above target

- Consider adding bezafibrate if triglycerides and LDLc are still above target despite above:
  - Target TG < 1.7 mmol/L if previous CV event or TG < 5.7 mmol/L if no previous CV event

MANAGEMENT OF CHRONIC KIDNEY DISEASE

- There are no changes from the impending new guidance on managing chronic kidney disease which is defined as albuminuria (UACR > 3 mg/mmol) and/or renal impairment (eGFR < 60 mL/min).

- Summary of key features:

- Start ACEi or ARB if no concerns over hypotension if any of:
  - UACR > 3 mg/mmol and eGFR > 15 mL/min
  - Diabetes mellitus (any type)
  - Titrate ACEi or ARB to maximal tolerated dose. If systolic BP remains ≥ 130 mmHg then add CCB or TD as outlined in management of elevated blood pressure.
- Start empagliflozin if eGFR > 20 mL/min and any of the following:
  - UACR > 20 mg/mmol
  - Type 2 diabetes with UACR > 3 mg/mmol and/or eGFR 20 – 60 mL/min
  - Heart failure
  - eGFR 20 – 44 mL/min at any level of albuminuria
- Start GLP1Ra if HbA1c above target and/or weight loss desirable
- Start lipid lowering therapy aiming for LDLc < 1.4 mmol/L if known CV disease or if high CV risk as per new criteria which includes:
  - Urinary ACR > 30 mg/mmol
  - eGFR < 45 mL/min
  - UACR 3 – 29 mg/mmol and eGFR 45 – 59 mL/min
  - Age > 50 years and UACR > 3 mg/mmol and/or eGFR < 60 mL/min
- Strongly consider lipid lowering therapy aiming for LDLc < 1.8 mmol/L if moderate CV risk
- Consider lipid lowering therapy aiming for LDLc < 1.8 mmol/L if 5 year CV risk 3 - 5% and risk factor(s) as per new criteria
- Risks of aspirin likely outweigh benefits in primary prevention of CV events in renal disease, but antiplatelet therapy for secondary prevention remains important

MANAGEMENT OF GOUT

- Management of gout is included in this guidance due to gout being common in people with CKM disease and that treatment of gout reduces CV events.

- There are no changes to the current recommended management of gout.

ANTIPLATELET THERAPY

- Antiplatelet therapy remains important for secondary prevention of CV events.

- Low dose aspirin for primary prevention is an individualised decision but the risks usually outweigh the benefits if any of the following:
  - 5 year CV risk is < 10%
  - > 70 years of age
  - Diabetes
  - Chronic kidney disease
  - High risk of bleeding

SCREENING FOR CKM DISEASE IN THE GENERAL POPULATION

- Opportunistic screening for CKM disease should be optimised wherever possible. Otherwise screening for CKM disease in the general population should occur at assessments for people with preclinical obesity or via the cardiovascular risk assessment (CVRA).

- CVRA should now be started at the following ages:
  - Men with any risk factors* - 30 years of age
  - Men without risk factors* – 40 years of age
  - Women with any risk factors* – 40 years of age
  - Women without risk factors* – 50 years of age
  - *Risk factors include:
    - Māori, Pacific, South-East Asian and other non-European ethnicities

        - Socioeconomic deprivation
        - Direct family history of CKM at < 40 years of age
        - Smoker
        - Post transplant
        - History of preeclampsia or gestational diabetes
        - Long term glucocorticoid and/or antipsychotic use
        - Chronic dental and/or peridontal disease
        - Clinical features of insulin resistance e.g. acanthosis nigricans, PCOS etc.

- If CKM disease is found⟶ optimise treatment as per guidance and repeat CVRA as part of regular CKM assessments.

- If no overt CKM disease ⟶ treatment and follow up is based on 5 year CV risk
    - Low CV risk (5 year CV risk < 5%) ⟶ repeat CVRA in 5 years
    - Moderate CV risk (5 year CV risk 5 - < 10%):
        - Consider lipid lowering therapy as per people with CKM disease
        - Repeat CVRA in 2 years
    - High CV risk (5 year CV risk ≥ 10%):
        - Start lipid lowering and antiplatelet therapy as per CKM disease
        - No need to repeat CVRA as should be optimising treatment at least yearly