



SESSIONE 1

**RISCHIO CARDIONEFROMETABOLICO NEL DIABETE TIPO 2**

**Il rischio **cardiorenale** ed aterosclerosi: un  
legame da non dimenticare**

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*Fondazione Policlinico Universitario Campus Bio-Medico di Roma*

12 Dicembre 2025

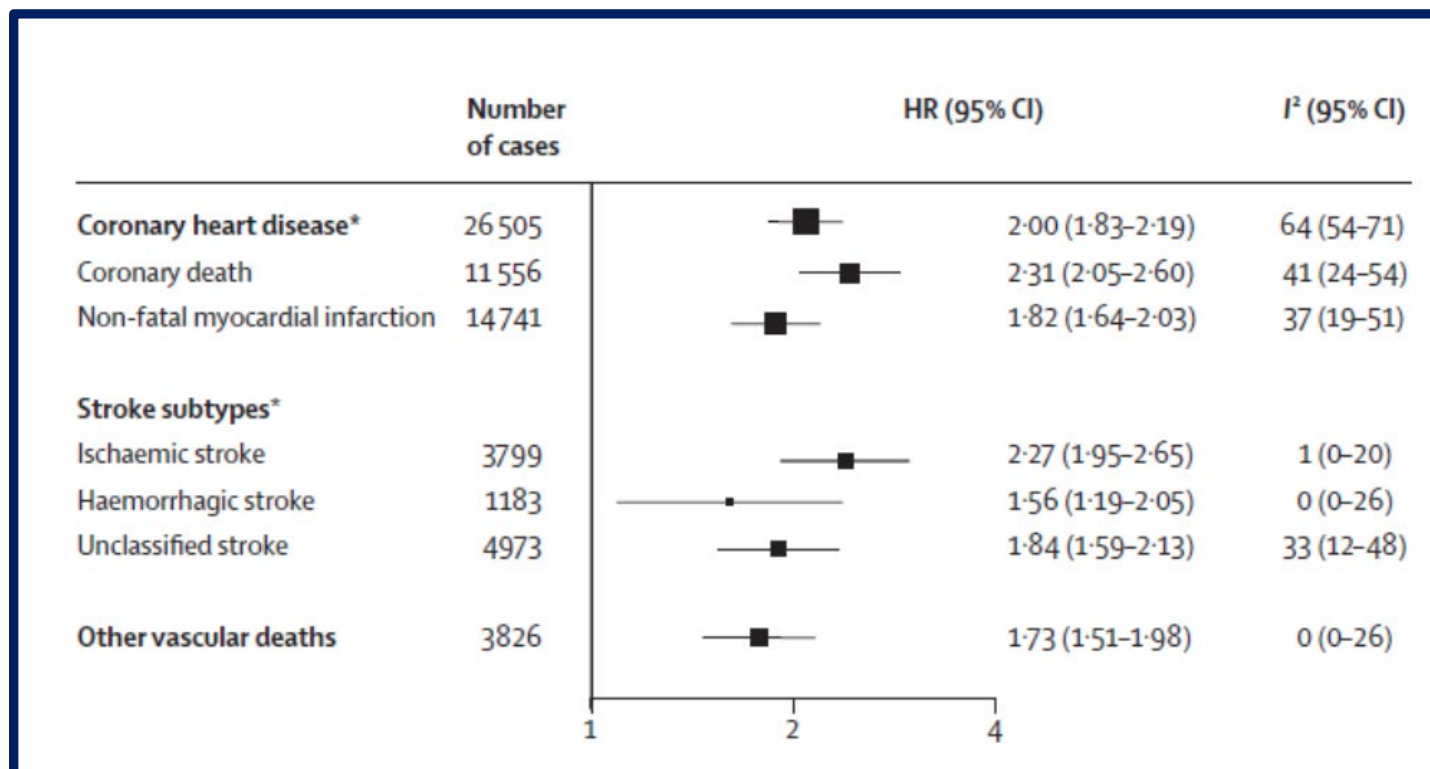
## **Conflict of interest:**

**Advisory board for Lilly**

**Institutional grant from AstraZeneca**

# Diabetes & Atherosclerotic Cardiovascular Disease Risk

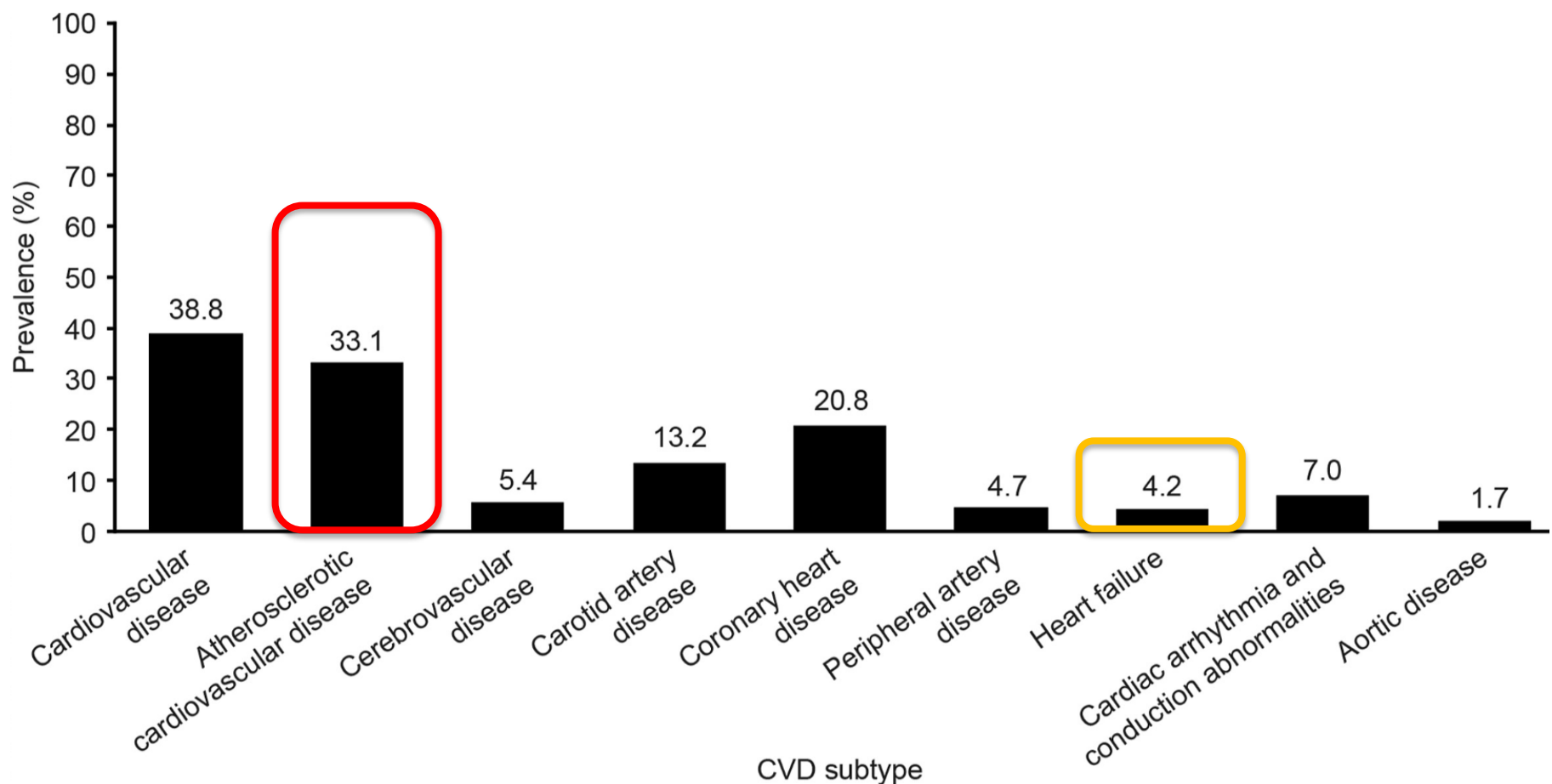
Diabetes confers a ~2-fold excess risk of CAD, ischemic stroke and vascular death



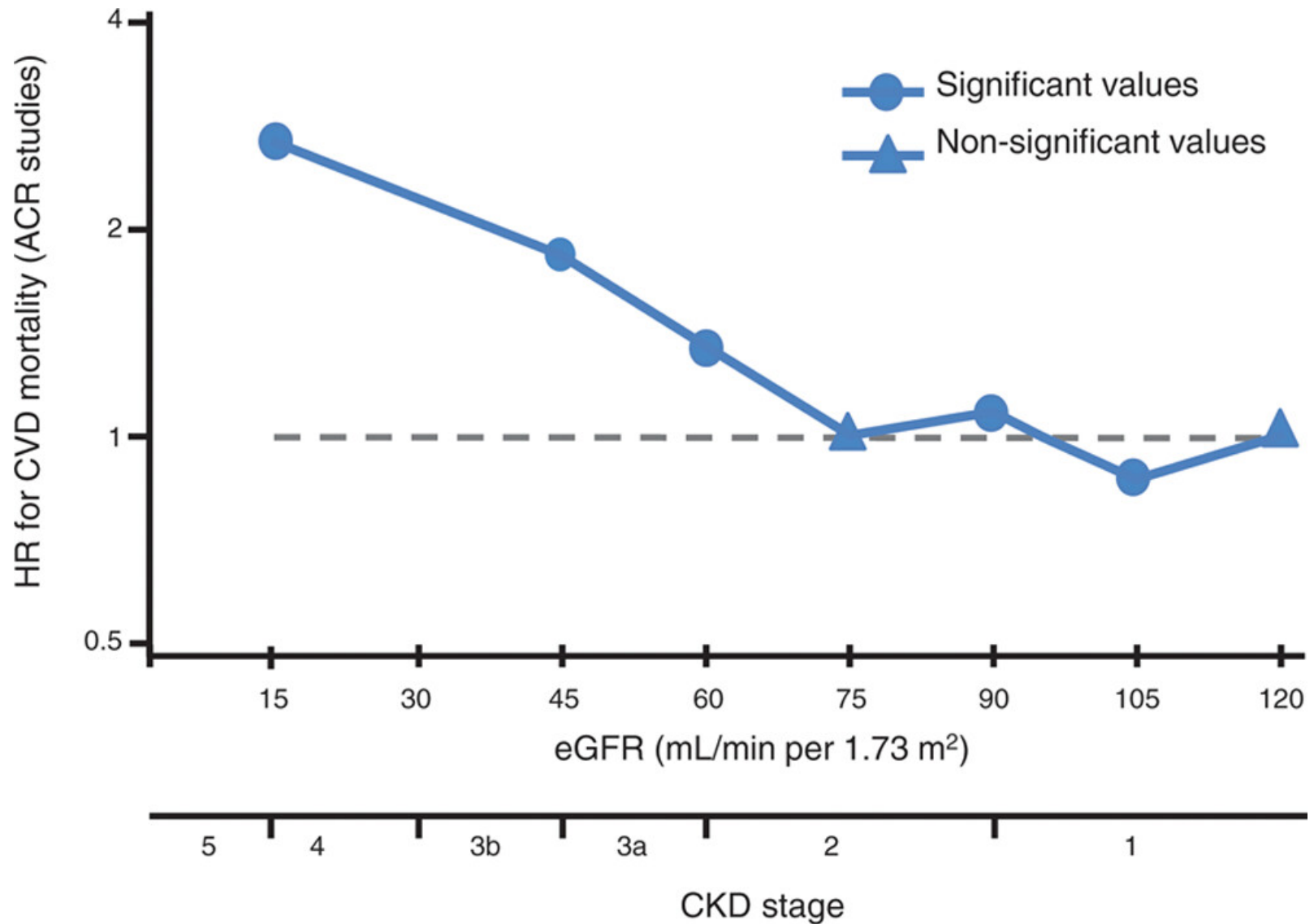
Collaborative meta-analysis of 102 studies

# Prevalence of Atherosclerotic Cardiovascular Disease in T2DM

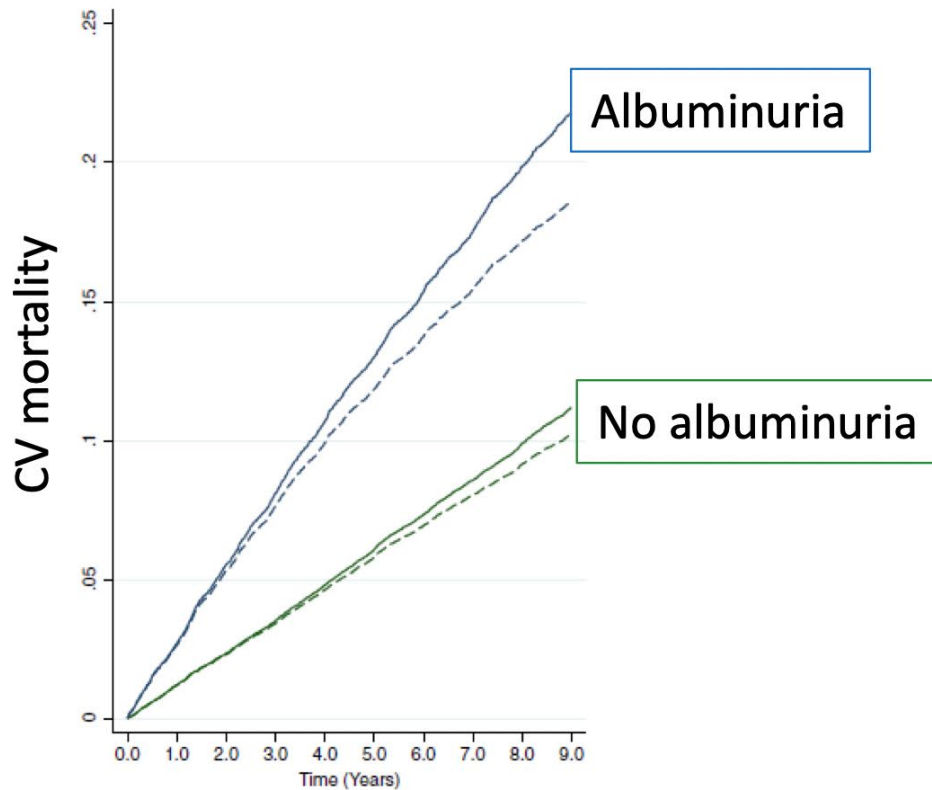
Italian Data



# Renal Disease Assessed by eGFR and CV Mortality

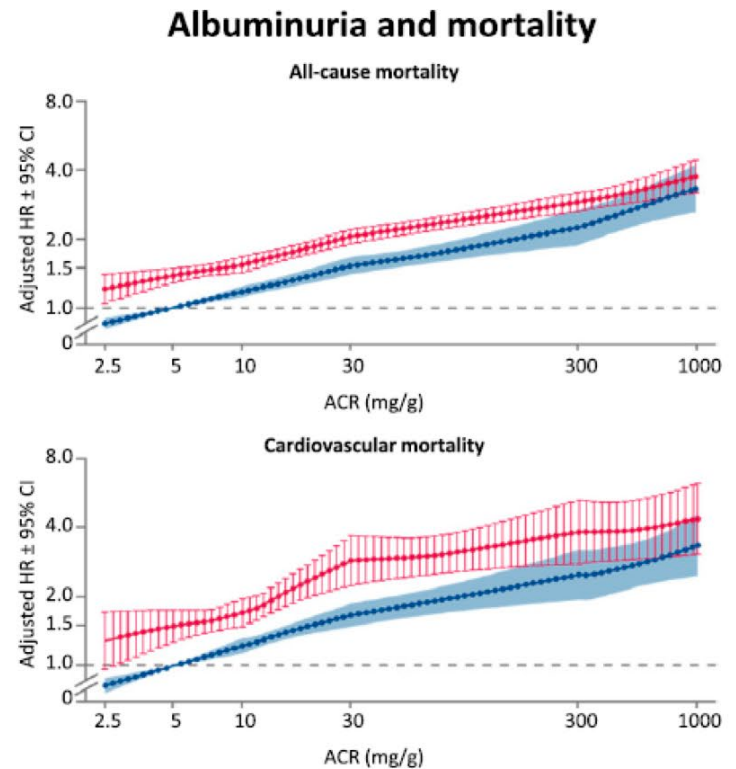


# Renal Disease Assessed by ACR and CV Mortality



*K-M with Cumulative risk estimates*

Feakins et al. Diag Prog Research 2018

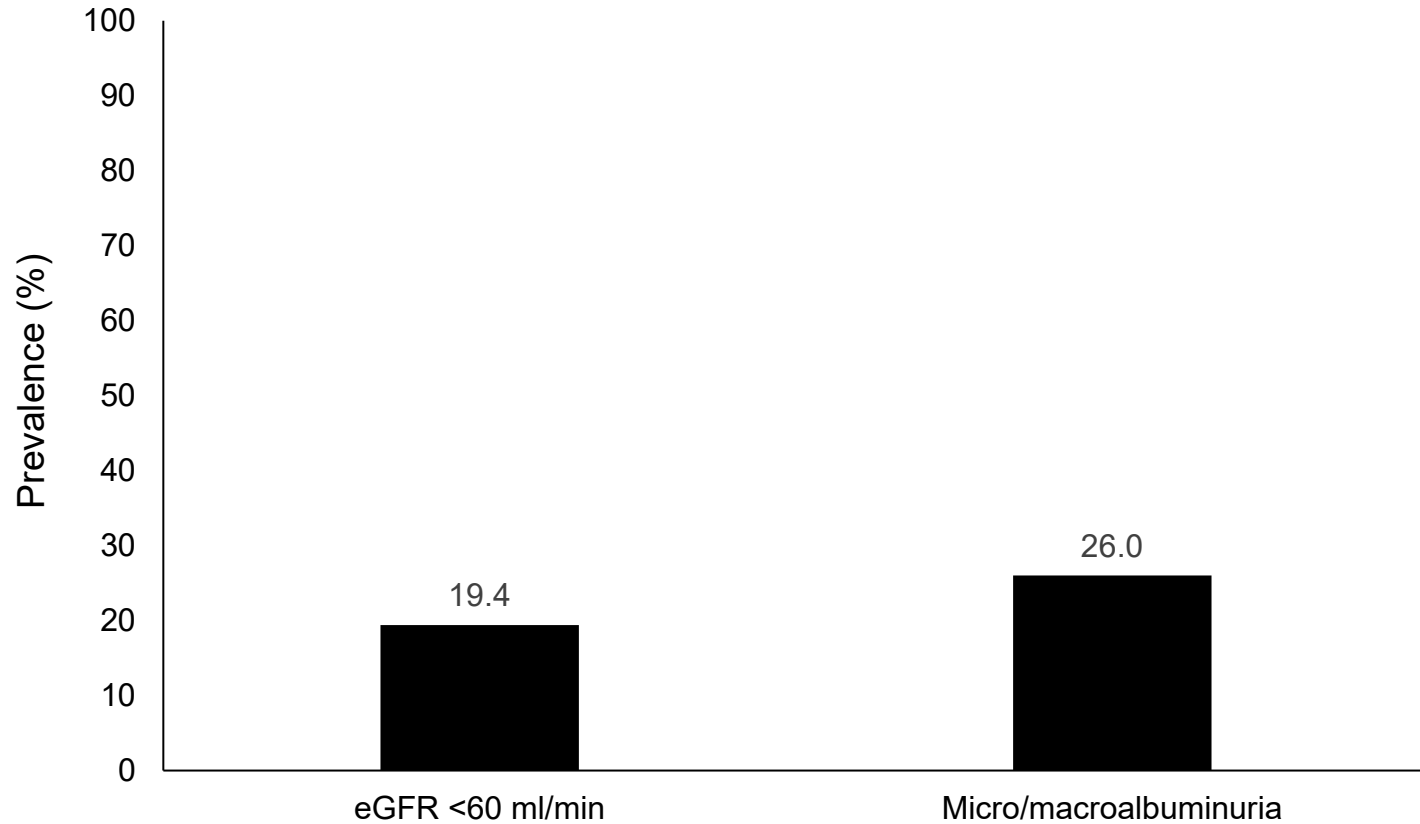


*HR for all-cause and CV mortality in participants with and without diabetes across the entire range of ACR.*

Fox et al. Lancet 2012

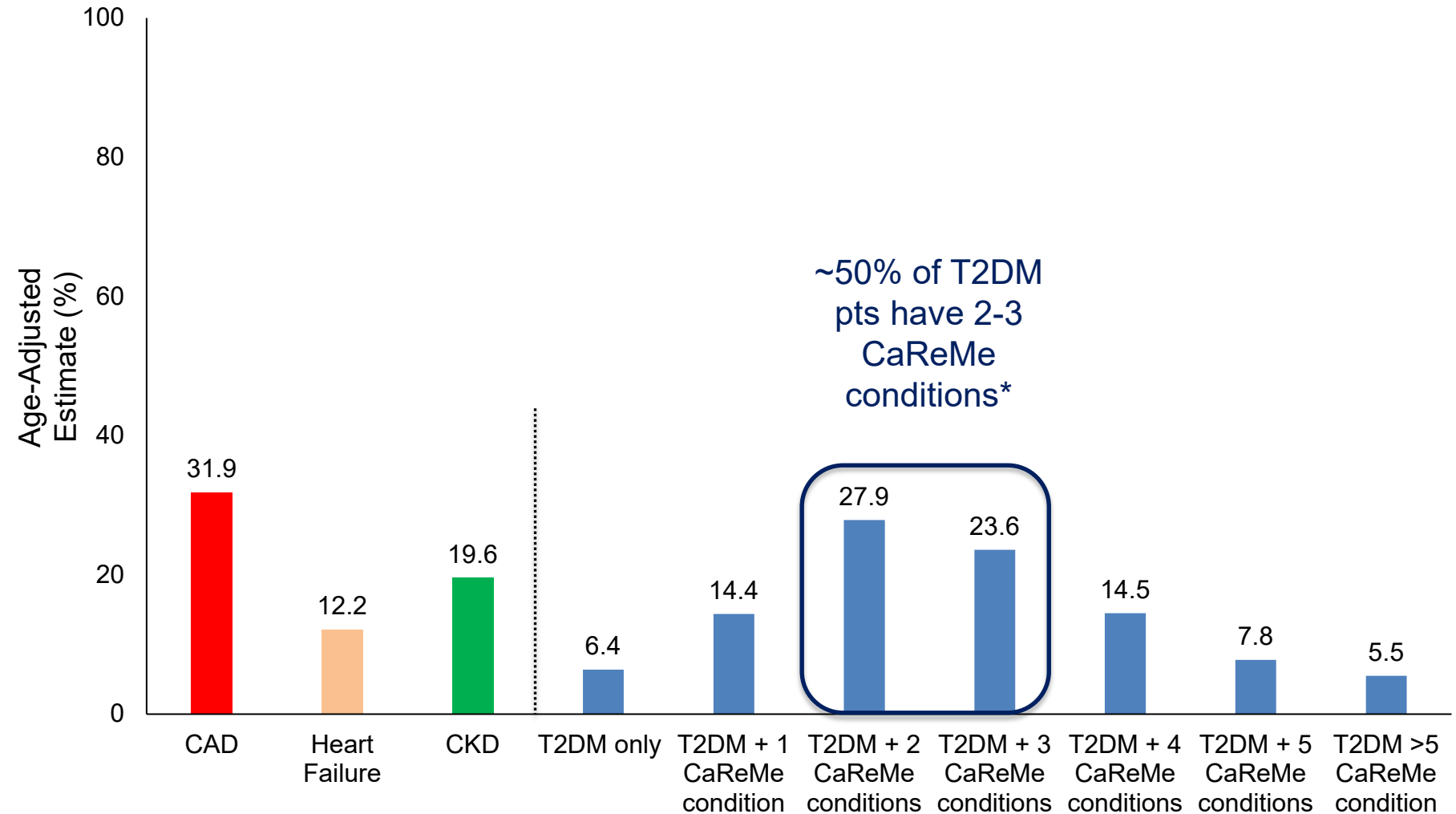
# Prevalence of Renal Disease in T2DM

Italian Data



# US Prevalence of **Cardio**-**Renal** Disease in T2DM

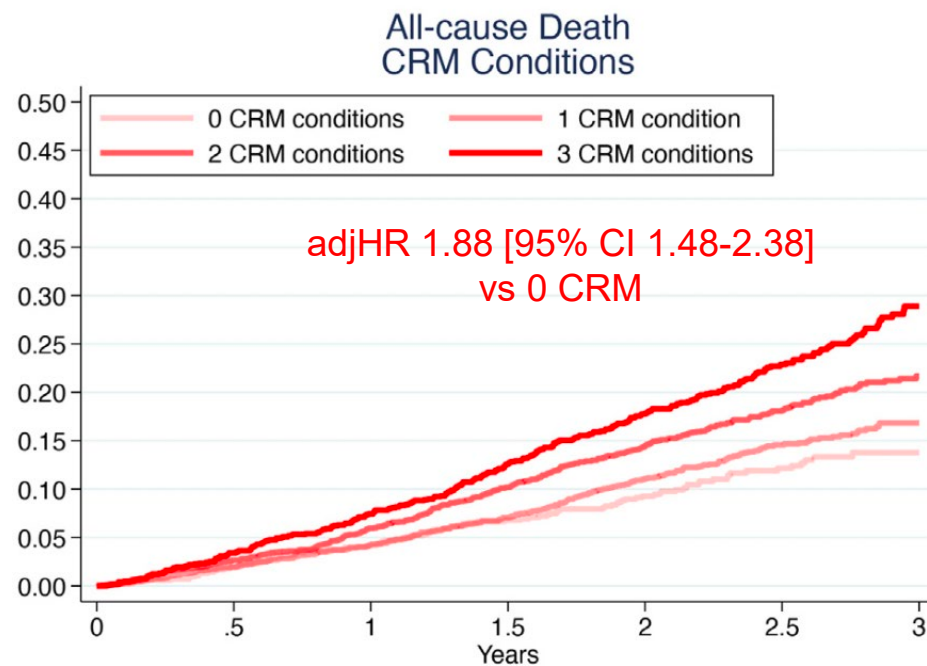
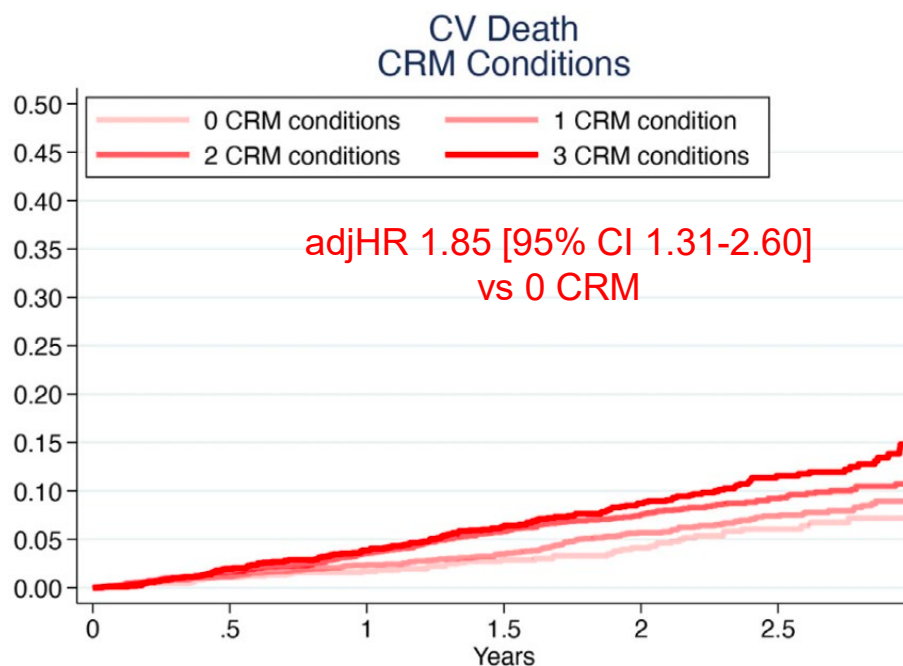
530,747 adults with T2DM in a US-based outpatient registry



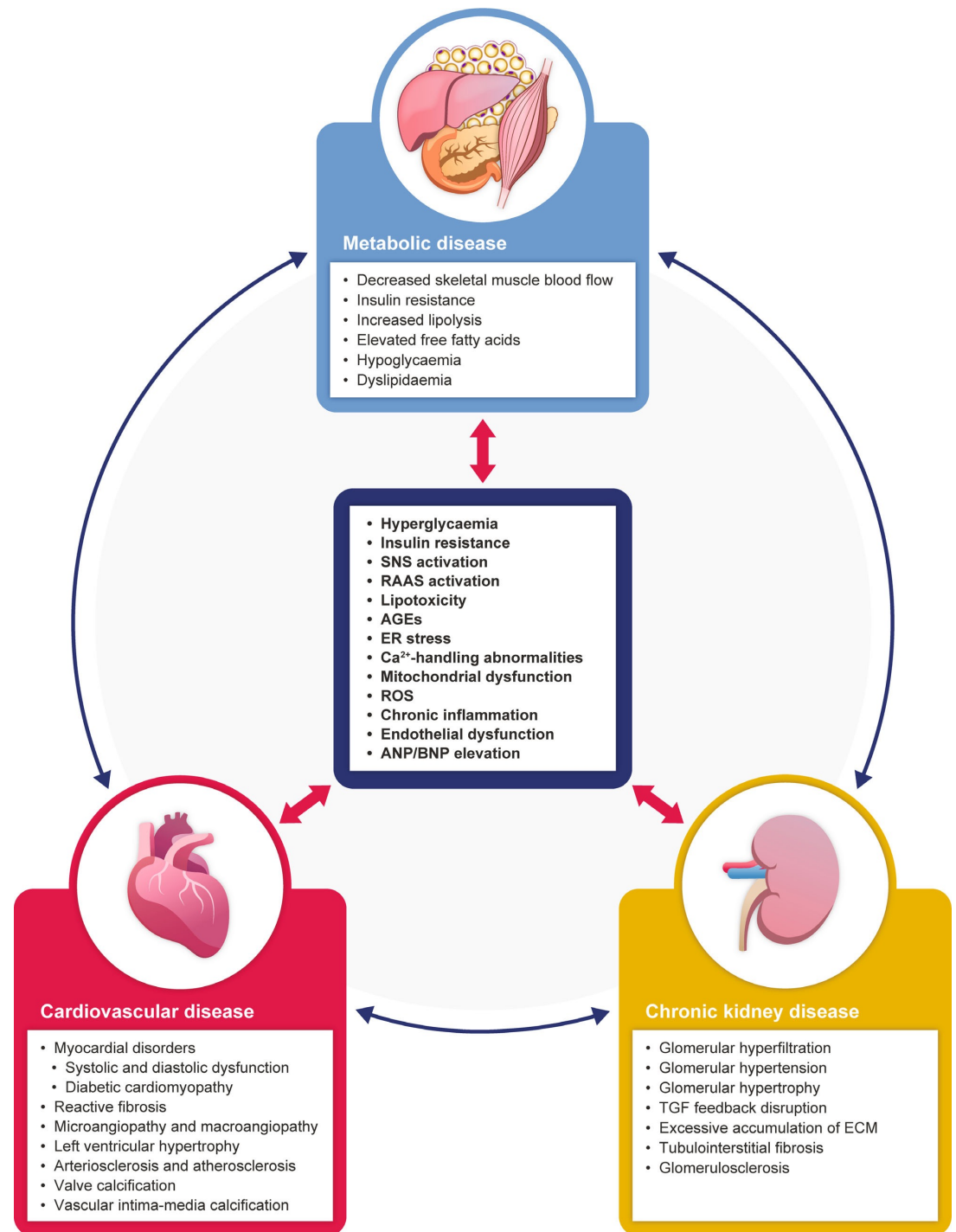
\*hypertension, hyperlipidaemia, CAD, CKD, cerebrovascular disease, PAD, AF, HF, hyperuricaemia

Arnold SV et al. Diabetes Obes Metab 2018

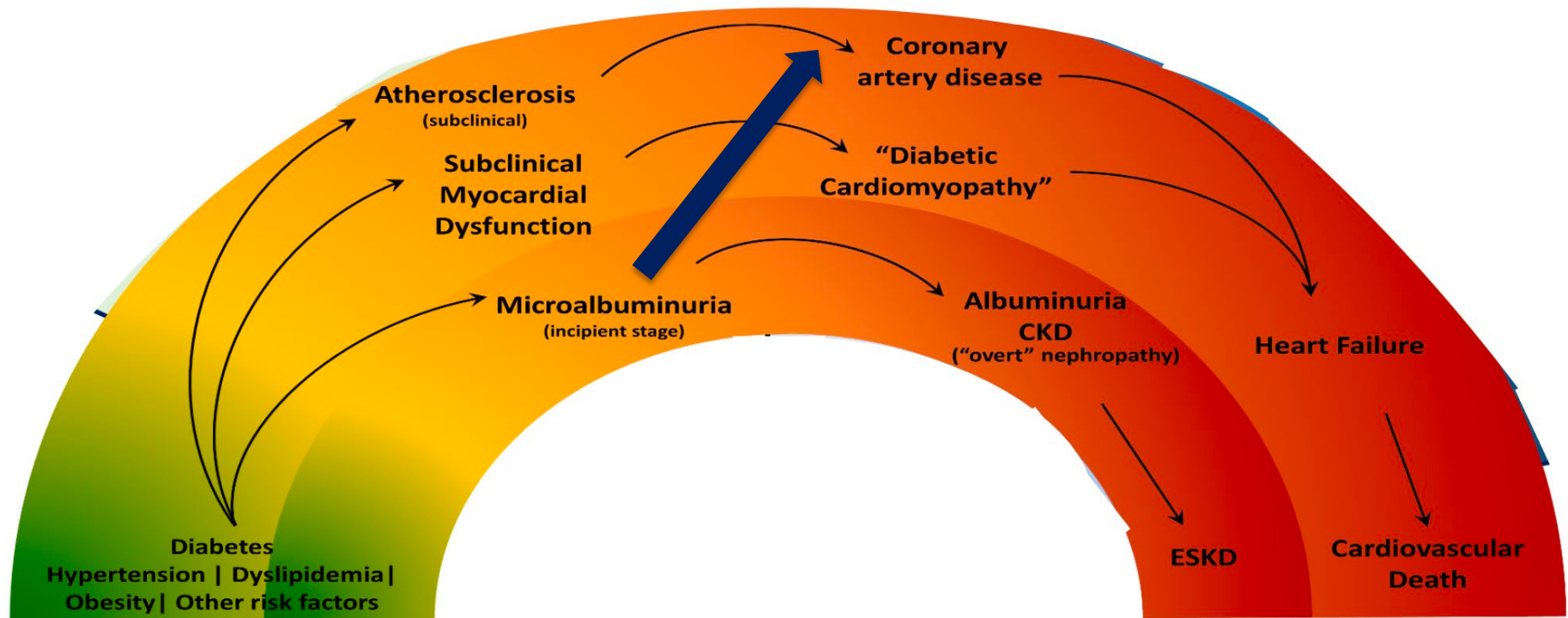
# Mortality by Number of Overlapping CRM Conditions



# Pathophysiological Interplay Between Cardiovascular, Kidney and Metabolic Disease



# Cardio-Renal Continuum



# ASCVD is the Major Cause of HF

## OpTIMa-HF Registry

HF outpatients' clinics of Italian hospitals and community HF outpatients' services

| Overall<br>( <i>n</i> = 2110)                   |             |
|-------------------------------------------------|-------------|
| Aetiology                                       |             |
| Ischaemic, <i>n</i> (%)                         | 1234 (58.6) |
| Idiopathic dilated cardiomyopathy, <i>n</i> (%) | 459 (21.8)  |
| Valvular heart disease, <i>n</i> (%)            | 131 (6.2)   |
| Hypertensive heart disease, <i>n</i> (%)        | 87 (4.1)    |
| Myocarditis, <i>n</i> (%)                       | 18 (0.9)    |
| Cardiotoxicity, <i>n</i> (%)                    | 24 (1.1)    |
| Other cardiomyopathies, <i>n</i> (%)            | 107 (5.1)   |
| Other causes, <i>n</i> (%)                      | 47 (2.2)    |

# Cardio-Renal Risk Stratification Tools in T2DM



Focus on ASCVD

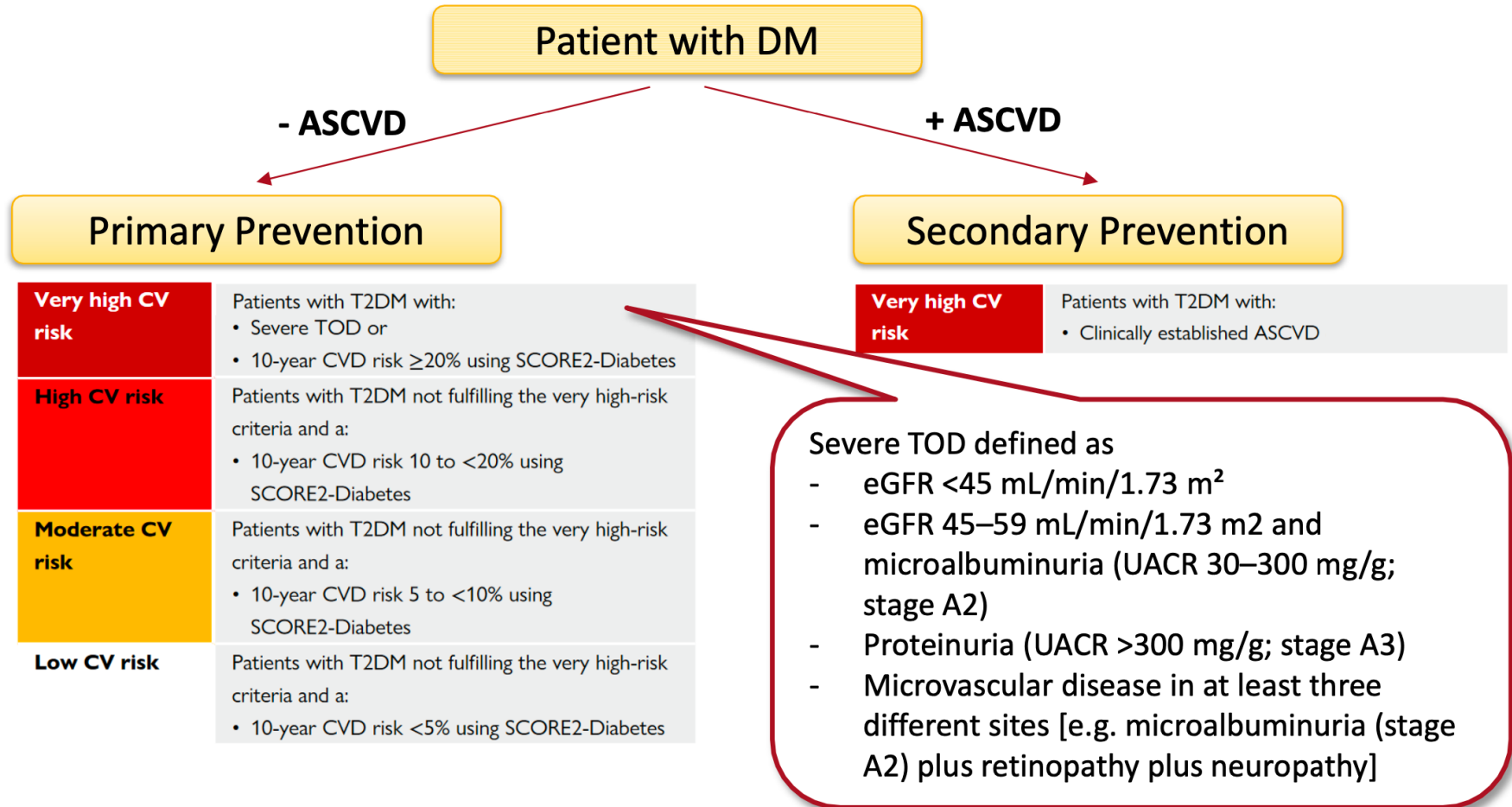
# Renal Disease Assessment and Prognosis

## KDIGO

| KDIGO: Prognosis of CKD by GFR and albuminuria categories             |     |                                  |       | Persistent albuminuria categories                    |                                                     |                                                |
|-----------------------------------------------------------------------|-----|----------------------------------|-------|------------------------------------------------------|-----------------------------------------------------|------------------------------------------------|
|                                                                       |     |                                  |       | Description and range                                |                                                     |                                                |
|                                                                       |     |                                  |       | A1                                                   | A2                                                  | A3                                             |
|                                                                       |     |                                  |       | Normal to mildly increased<br><30 mg/g<br><3 mg/mmol | Moderately increased<br>30–300 mg/g<br>3–30 mg/mmol | Severely increased<br>>300 mg/g<br>>30 mg/mmol |
| GFR categories (ml/min/1.73 m <sup>2</sup> )<br>Description and range | G1  | Normal or high                   | ≥90   |                                                      |                                                     |                                                |
|                                                                       | G2  | Mildly decreased                 | 60–89 |                                                      |                                                     |                                                |
|                                                                       | G3a | Mildly to moderately decreased   | 45–59 |                                                      |                                                     |                                                |
|                                                                       | G3b | Moderately to severely decreased | 30–44 |                                                      |                                                     |                                                |
|                                                                       | G4  | Severely decreased               | 15–29 |                                                      |                                                     |                                                |
|                                                                       | G5  | Kidney failure                   | <15   |                                                      |                                                     |                                                |

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk; GFR, glomerular filtration rate.

# ASCVD Risk Assessment in T2DM



# SCORE2-Diabetes

## Recommendation

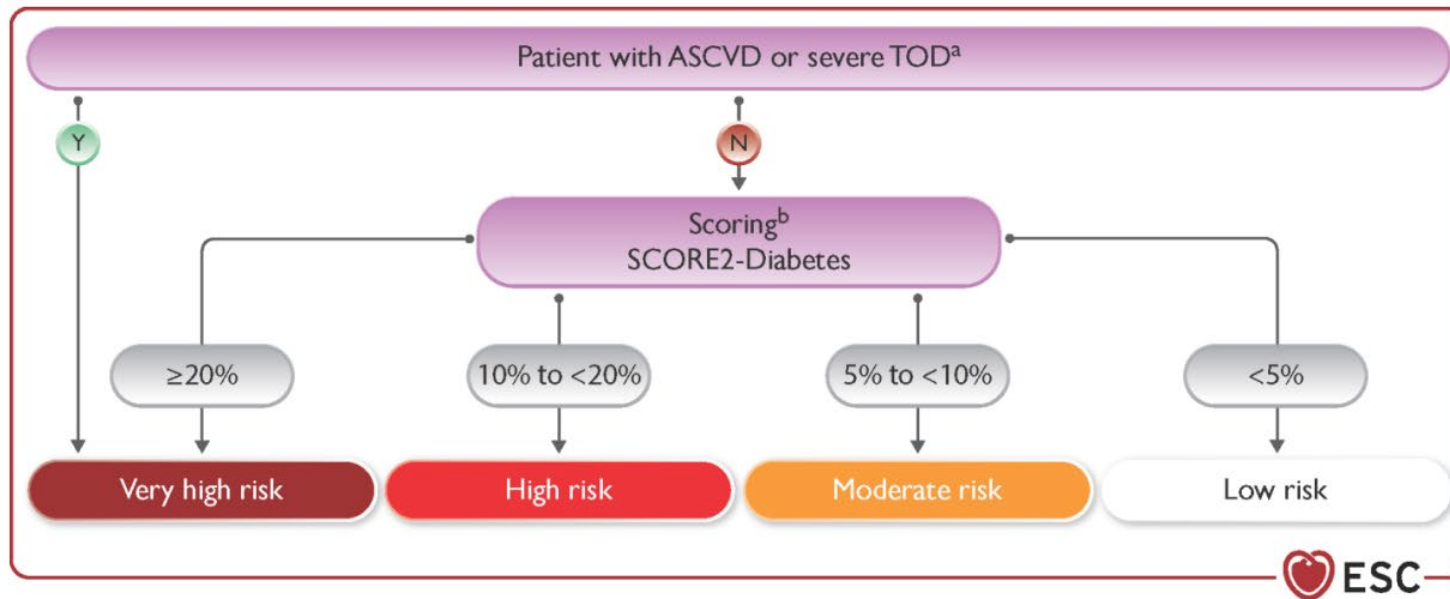
In patients with T2DM without symptomatic ASCVD or severe TOD, it is recommended to estimate 10-year CVD risk via SCORE2-Diabetes.

**Class**

**I**

**Level**

**B**



a  $\geq 40 - 69$  years

## How to Calculate Total CV Risk with SCORE2-Diabetes

Points table for men with diabetes and current age 40–69 years

Risk predictor

Age of diabetes diagnosis (years)

Smoking status

Systolic blood pressure (mmHg)

Total cholesterol (mmol/L)

HDL cholesterol (mmol/L)

HbA1c (mmol/mol)

eGFR (mL/min/1.73 m²)

Points total:

Risk region

Points total

Low-risk region

Moderate-risk region

High-risk region

Very high-risk region

Low-risk region

Moderate-risk region

High-risk region

Very high-risk region

Low-risk region

Moderate-risk region

High-risk region

Very high-risk region

Low-risk region

Moderate-risk region

High-risk region

Very high-risk region

30–39

40–49

50–59

60–69

≥70

30–44

45–59

60–89

≥90

Men with diabetes. Risk Table: 10-year CVD risk estimate corresponding to each total score

Current age between 40 and 54 years

Current age between 55 and 69 years

Women with diabetes. Risk Table: 10-year CVD risk estimate corresponding to each total score

Current age between 40 and 54 years

Current age between 55 and 69 years

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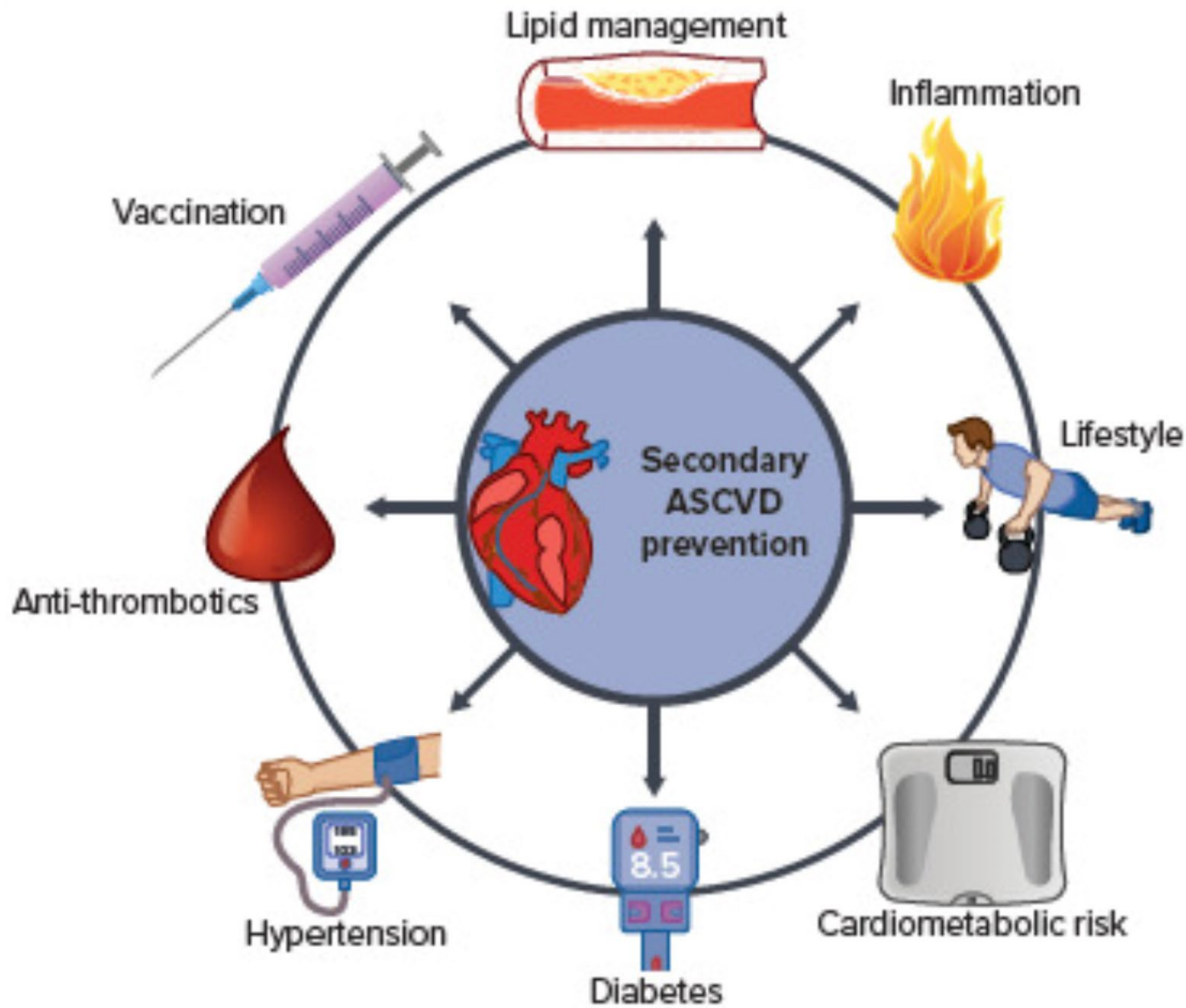
3

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**Better use the ESC CVD Risk Calculation App...**

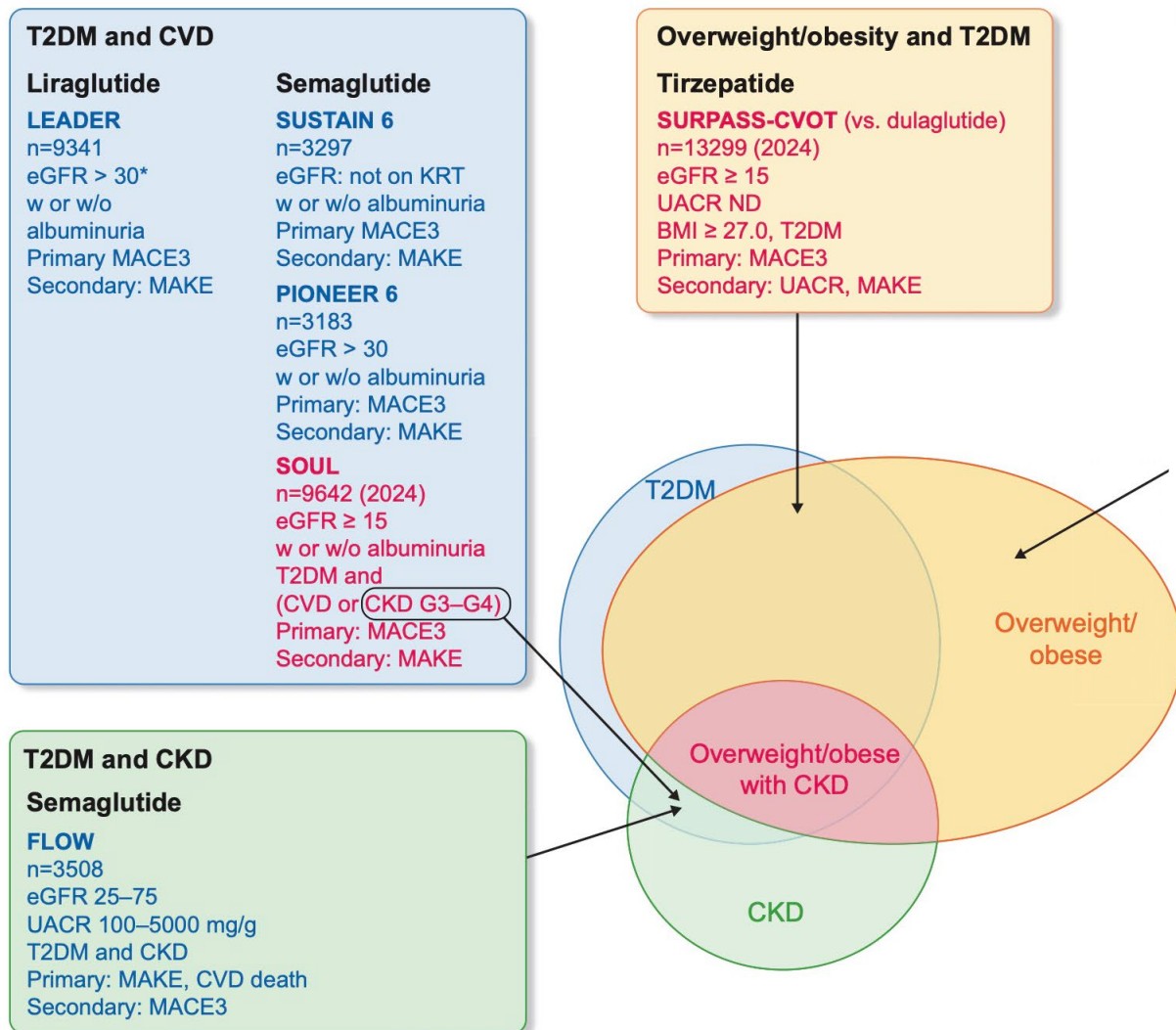
# Therapeutic Pillars for ASCVD ( $\pm$ T2DM/CKD)



# Medications with **Cardiorenal** Protective Effects

|  <b>Renal Outcomes</b>                                                                      | <b>Potential Mechanisms</b>                                                                                                                                                                                 |  <b>Medication</b> | <b>Potential Mechanisms</b>                                                                                                                                                                                     |  <b>Cardiovascular Outcomes</b>          |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>↓ Composite of dialysis, transplant, or death due to kidney disease</li> <li>↓ ESRD</li> <li>↓ AKI</li> </ul>                        | <ul style="list-style-type: none"> <li>↑ Vasoconstriction of afferent arteriole and decreased hyperfiltration, barotrauma, and proteinuria</li> <li>↓ Oxidative stress</li> <li>↓ Blood pressure</li> </ul> | <b>SGLT2 inhibitors</b>                                                                             | <ul style="list-style-type: none"> <li>↓ Plasma volume, arterial stiffness, and blood pressure</li> <li>↓ Oxidative stress</li> <li>↑ Sensitivity to diuretics and natriuretic peptides</li> </ul>              | <ul style="list-style-type: none"> <li>↓ CV death</li> <li>↓ MI</li> <li>↓ HHF</li> <li>↔ Stroke</li> </ul>                 |
| <ul style="list-style-type: none"> <li>↓ Composite of development of new onset macroalbuminuria, decline in eGFR, ESRD, or death due to kidney disease</li> </ul>           | <ul style="list-style-type: none"> <li>↓ Blood pressure</li> <li>↓ Weight</li> <li>↓ Dyslipidemia</li> <li>↓ Oxidative stress</li> <li>↓ Endothelial dysfunction</li> </ul>                                 | <b>GLP-1 receptor agonists</b>                                                                      | <ul style="list-style-type: none"> <li>↓ Blood pressure</li> <li>↓ Weight</li> <li>↓ Dyslipidemia</li> <li>↓ Oxidative stress</li> <li>↓ Endothelial dysfunction</li> </ul>                                     | <ul style="list-style-type: none"> <li>↓ CV death</li> <li>↓ MI</li> <li>↓ HF</li> <li>↓ Stroke</li> </ul>                  |
| <ul style="list-style-type: none"> <li>↓ Composite of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes</li> </ul> | <ul style="list-style-type: none"> <li>↓ Inflammation</li> <li>↓ Fibrosis</li> <li>↓ Blood pressure</li> <li>↓ Endothelial dysfunction</li> <li>↓ Tissue remodeling</li> <li>↓ Proteinuria</li> </ul>       | <b>Selective nonsteroidal MR antagonists</b>                                                        | <ul style="list-style-type: none"> <li>↓ Inflammation</li> <li>↓ Fibrosis</li> <li>↓ Blood pressure</li> <li>↓ Endothelial dysfunction</li> <li>↓ Tissue remodeling</li> </ul>                                  | <ul style="list-style-type: none"> <li>↓ Composite of death from CV causes, nonfatal MI, nonfatal stroke, or HHF</li> </ul> |
| <ul style="list-style-type: none"> <li>↓ Onset of microalbuminuria</li> <li>↓ Progression to macroalbuminuria</li> <li>↓ ESRD</li> </ul>                                    | <ul style="list-style-type: none"> <li>↓ Blood pressure</li> <li>↓ Endothelial dysfunction</li> <li>↓ Vasoconstriction of efferent arteriole and decreased hyperfiltration</li> </ul>                       | <b>RAAS inhibitors</b>                                                                              | <ul style="list-style-type: none"> <li>↓ Blood pressure</li> <li>↓ Vasoconstriction of coronary arteries</li> <li>↓ Atherosclerosis</li> <li>↓ Endothelial dysfunction</li> <li>↓ Cardiac remodeling</li> </ul> | <ul style="list-style-type: none"> <li>↓ MI</li> <li>↓ HHF</li> </ul>                                                       |

# Key Phase 3 RCT With **Kidney** or **Cardiovascular** Primary Outcomes of GLP-1 RA Approved for the Treatment of T2DM



# Clinical Evidence of **Cardiovascular** Protection

a Meta-Analysis of RCT (11 Trials; 85,373 Patients)

## MACE

GLP-1 receptor agonist  
(n/N [%])

Placebo  
(n/N [%])

Hazard ratio  
(95% CI)

Weight  
(%)

### With diabetes

|                                |                   |                    |                                                                                     |                                    |        |
|--------------------------------|-------------------|--------------------|-------------------------------------------------------------------------------------|------------------------------------|--------|
| EXSC <sup>40</sup>             | 839/7356 (11.4%)  | 905/7396 (12.2%)   |  | 0.91 (0.83–1.00)                   | 14.51% |
| LEADER <sup>24,33</sup>        | 608/4668 (13.0%)  | 694/4672 (14.9%)   |  | 0.87 (0.78–0.97)                   | 13.06  |
| REWIND <sup>23,35</sup>        | 594/4949 (12.0%)  | 663/4952 (13.4%)   |  | 0.88 (0.79–0.99)                   | 12.72% |
| ELIXA <sup>37</sup>            | 400/3034 (13.2%)  | 392/3034 (12.9%)   |  | 1.02 (0.89–1.17)                   | 10.76% |
| Harmony Outcomes <sup>38</sup> | 338/4731 (7.1%)   | 428/4732 (9.0%)    |  | 0.78 (0.68–0.90)                   | 10.51% |
| FLOW <sup>26</sup>             | 212/1767 (12.0%)  | 254/1766 (14.4%)   |  | 0.79 (0.66–0.94)                   | 8.13%  |
| AMPLITUDE-O <sup>39</sup>      | 189/2717 (7.0%)   | 125/1359 (9.2%)    |  | 0.73 (0.58–0.92)                   | 5.70%  |
| SUSTAIN-6 <sup>25,41</sup>     | 108/1648 (6.6%)   | 146/1649 (8.9%)    |  | 0.74 (0.58–0.95)                   | 5.16%  |
| FREEDOM-CVO <sup>36</sup>      | 85/2075 (4.1%)    | 69/2081 (3.3%)     |  | 1.24 (0.90–1.70)                   | 3.45%  |
| PIONEER 6 <sup>34</sup>        | 61/1591 (3.8%)    | 76/1592 (4.8%)     |  | 0.79 (0.57–1.10)                   | 3.19%  |
| Subtotal                       | 3434/34536 (9.9%) | 3752/33233 (11.3%) |  | <b>-13% RR</b><br>0.87 (0.81–0.93) |        |

### Without diabetes

|                         |                   |                    |                                                                                       |                  |        |
|-------------------------|-------------------|--------------------|---------------------------------------------------------------------------------------|------------------|--------|
| SELECT <sup>27,42</sup> | 569/8803 (6.5%)   | 701/8801 (8%)      |   | 0.80 (0.72–0.89) | 12.83% |
|                         |                   |                    |  | 0.80 (0.72–0.89) |        |
| Overall                 | 4003/43339 (9.2%) | 4453/42034 (10.6%) |  | 0.86 (0.80–0.92) |        |

With diabetes  $p < 0.001$ ,  $I^2 = 49.75\%$

Without diabetes  $p < 0.001$

Overall  $p < 0.001$ ,  $I^2 = 48.9\%$

Heterogeneity by diabetes status  $p = 0.24$



# Clinical Evidence of **Cardiovascular** Protection

a Meta-Analysis of RCT (11 Trials; 85,373 Patients)

## CV Death

### With diabetes

|                                |                    |                    |                                                                                     |                  |        |
|--------------------------------|--------------------|--------------------|-------------------------------------------------------------------------------------|------------------|--------|
| EXSCEL <sup>40</sup>           | 340/7356 (4.6%)    | 383/7396 (5.2%)    |  | 0.88 (0.76-1.02) | 20.11% |
| REWIND <sup>23,35</sup>        | 317/4949 (6.4%)    | 346/4952 (7.0%)    |  | 0.91 (0.78-1.06) | 18.50% |
| LEADER <sup>24,33</sup>        | 219/4668 (4.7%)    | 278/4672 (6.0%)    |  | 0.78 (0.66-0.93) | 14.80% |
| ELIXA <sup>37</sup>            | 156/3034 (5.1%)    | 158/3034 (5.2%)    |  | 0.98 (0.78-1.23) | 8.70%  |
| FLOW <sup>26</sup>             | 123/1767 (7.0%)    | 169/1766 (9.6%)    |  | 0.71 (0.56-0.90) | 8.11%  |
| Harmony Outcomes <sup>38</sup> | 122/4731 (2.6%)    | 130/4732 (2.7%)    |  | 0.93 (0.73-1.19) | 7.29%  |
| AMPLITUDE-O <sup>39</sup>      | 75/2717 (2.8%)     | 50/1359 (3.7%)     |  | 0.72 (0.50-1.03) | 3.33%  |
| SUSTAIN-6 <sup>25,41</sup>     | 44/1648 (2.7%)     | 46/1649 (2.8%)     |  | 0.98 (0.65-1.48) | 2.57%  |
| FREEDOM-CVO <sup>36</sup>      | 28/2075 (1.3%)     | 23/2081 (1.1%)     |  | 1.22 (0.70-2.12) | 1.42%  |
| PIONEER 6 <sup>34</sup>        | 15/1591 (0.9%)     | 30/1592 (1.9%)     |   | 0.49 (0.27-0.90) | 1.16%  |
| Subtotal                       | 1439/34 536 (4.2%) | 1613/33 233 (4.9%) |  | 0.86 (0.80-0.92) |        |

**-14% RR**

### Without diabetes

|                         |                    |                    |                                                                                       |                  |        |
|-------------------------|--------------------|--------------------|---------------------------------------------------------------------------------------|------------------|--------|
| SELECT <sup>27,42</sup> | 223/8803 (2.5%)    | 262/8801 (3%)      |    | 0.85 (0.71-1.01) | 14.01% |
| Overall                 | 1662/43 339 (3.8%) | 1885/42 034 (4.5%) |  | 0.86 (0.80-0.92) |        |

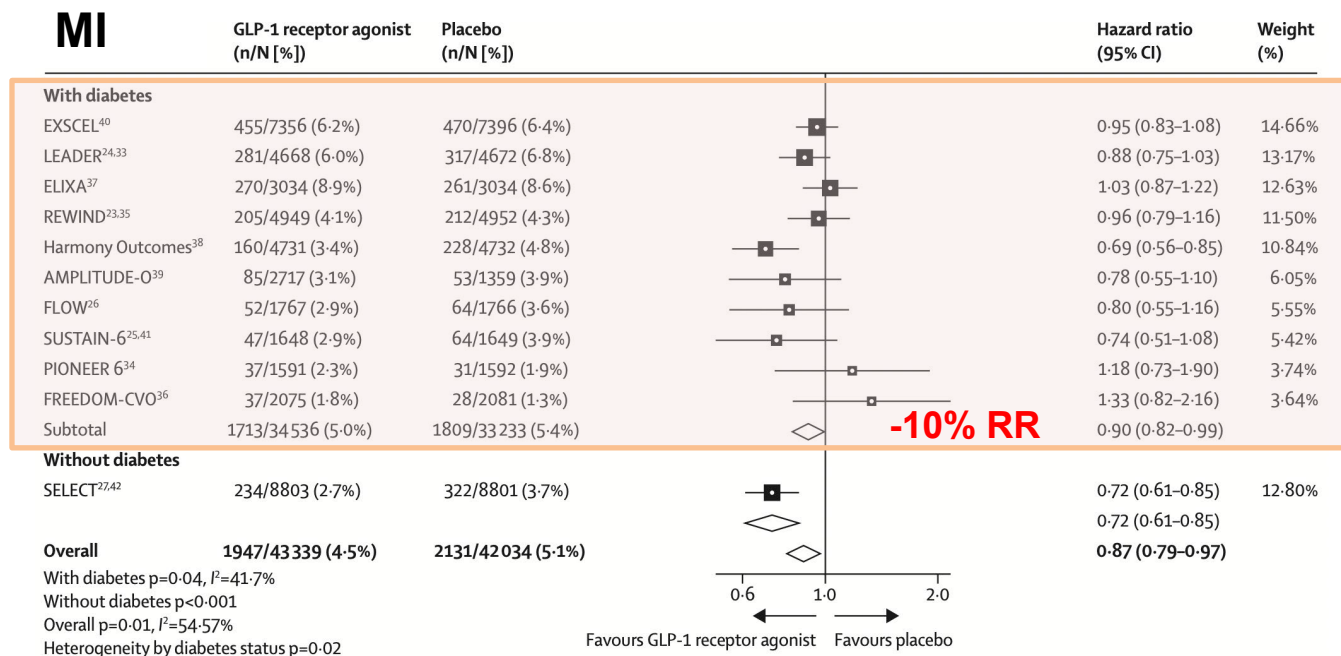
With diabetes  $p < 0.001$ ,  $I^2 = 4.77\%$

Without diabetes  $p = 0.07$

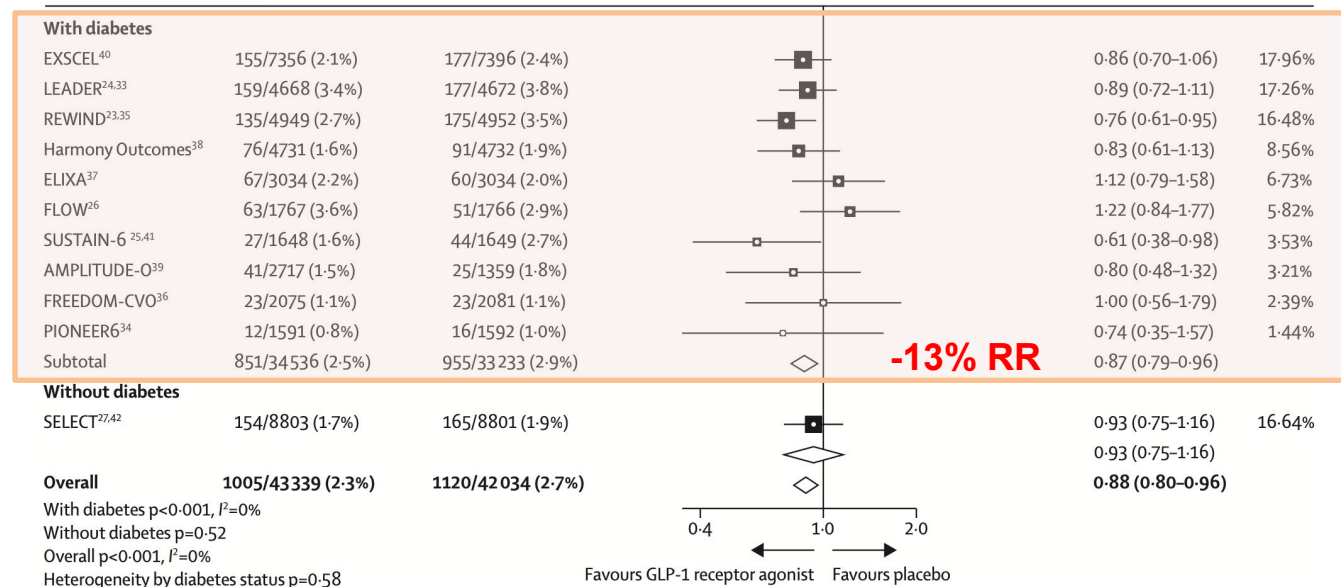
Overall  $p < 0.001$ ,  $I^2 = 0\%$

Heterogeneity by diabetes status  $p = 0.93$





## Stroke



# Subgroup Analysis

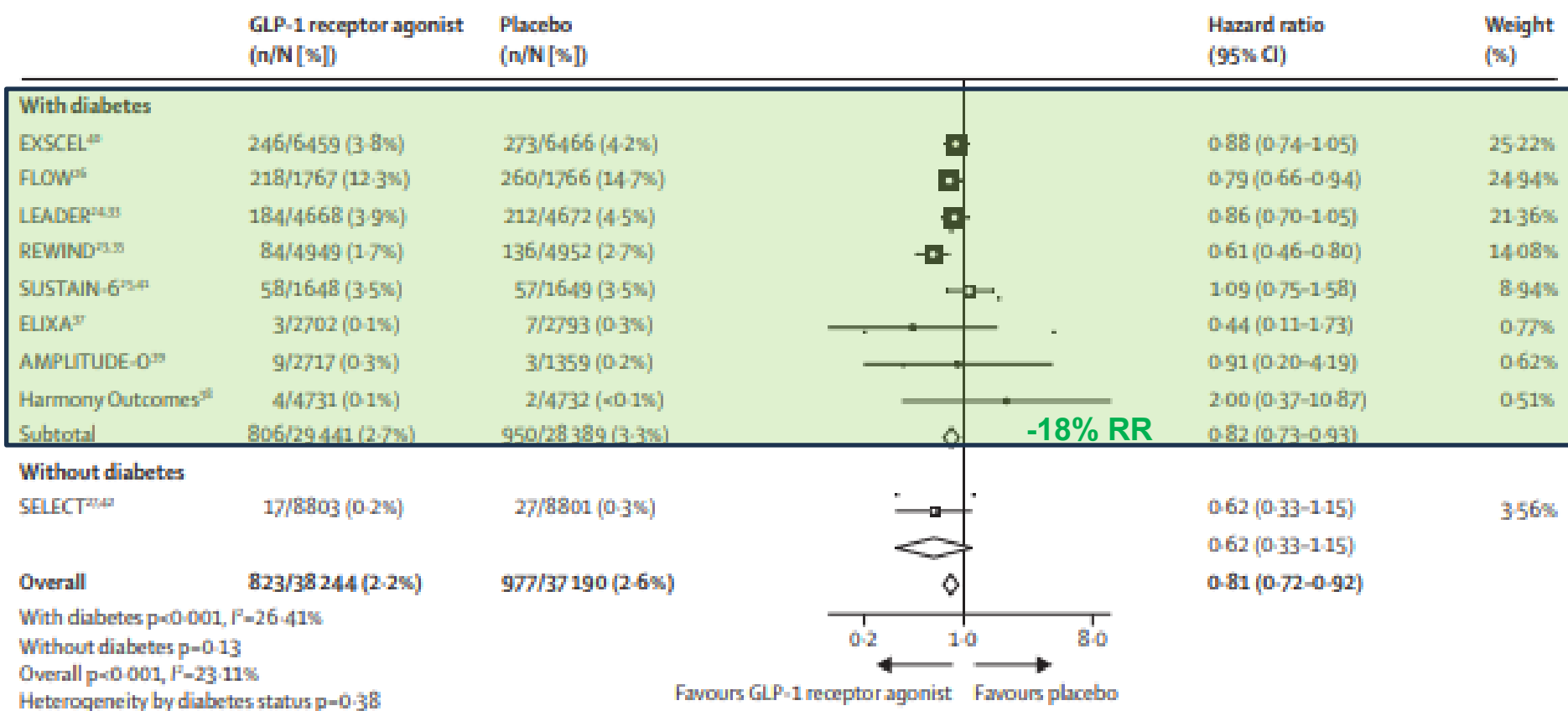
## MACE

|             |    | GLP-1 RA (n/N)     | Placebo (n/N)      |  | HR (95% CI)      | I <sup>2</sup> % | P-int |
|-------------|----|--------------------|--------------------|--|------------------|------------------|-------|
| <b>Sex</b>  |    |                    |                    |  |                  |                  |       |
| Male        | 10 | 2731/27172 (10.1%) | 2978/26341 (11.3%) |  | 0.88 (0.81-0.96) | 52.1%            | 0.41  |
| Female      | 10 | 1076/14400 (7.5%)  | 1238/13927 (8.9%)  |  | 0.84 (0.77-0.91) | 0%               |       |
| <b>Age</b>  |    |                    |                    |  |                  |                  |       |
| <65 years   | 10 | 1689/22170 (7.6%)  | 1832/21355 (8.6%)  |  | 0.84 (0.75-0.94) | 59.1%            | 0.75  |
| ≥65 years   | 10 | 2118/19402 (10.9%) | 2384/18923 (12.6%) |  | 0.86 (0.81-0.92) | 14.0%            |       |
| <b>BMI</b>  |    |                    |                    |  |                  |                  |       |
| <30         | 10 | 1449/15927 (9.1%)  | 2150/18135 (11.9%) |  | 0.82 (0.73-0.93) | 63.2%            | 0.34  |
| ≥30         | 10 | 2336/25524 (9.2%)  | 2539/24701 (10.3%) |  | 0.88 (0.83-0.93) | 2.2%             |       |
| <b>CVD</b>  |    |                    |                    |  |                  |                  |       |
| Yes         | 9  | 3177/32476 (9.8%)  | 3578/31233 (11.5%) |  | 0.84 (0.78-0.90) | 48.4%            | 0.13  |
| No          | 6  | 492/6725 (7.3%)    | 521/6684 (7.8%)    |  | 0.96 (0.82-1.12) | 15.9%            |       |
| <b>eGFR</b> |    |                    |                    |  |                  |                  |       |
| ≥60         | 10 | 2420/30545 (7.9%)  | 2706/29618 (9.1%)  |  | 0.85 (0.78-0.93) | 53.4%            | 0.94  |
| <60         | 10 | 986/7729 (12.8%)   | 1088/7356 (14.8%)  |  | 0.85 (0.74-0.97) | 48.8%            |       |

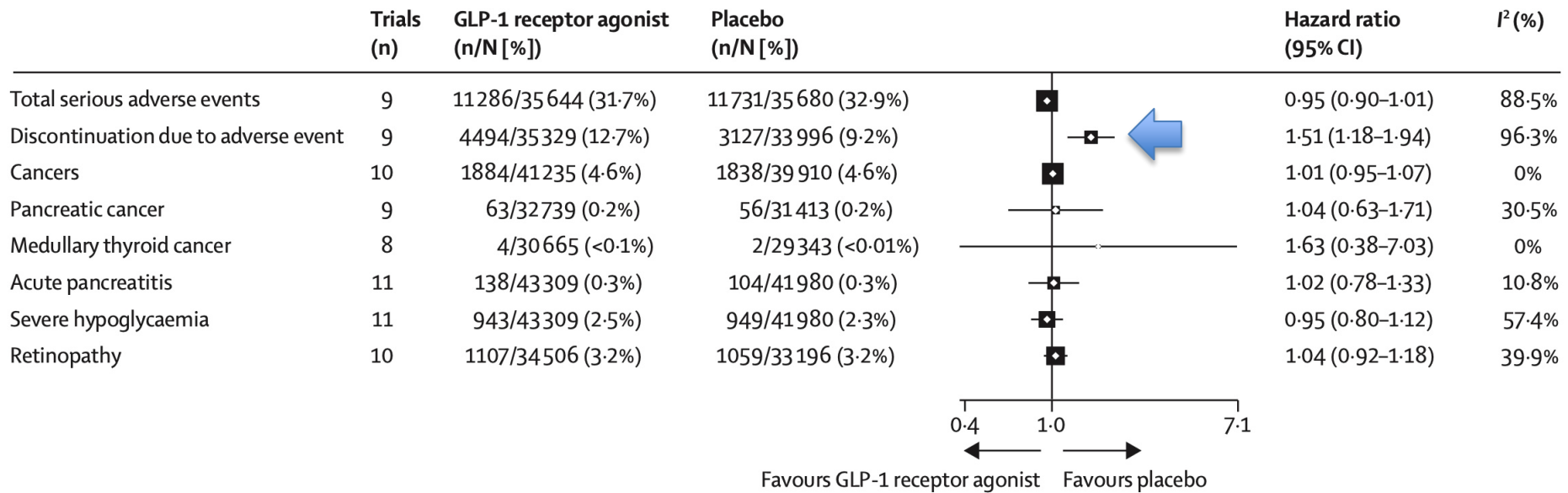
# Clinical Evidence of Renal Protection

a Meta-Analysis of RCT (11 Trials; 85,373 Patients)

## Composite Kidney Outcome



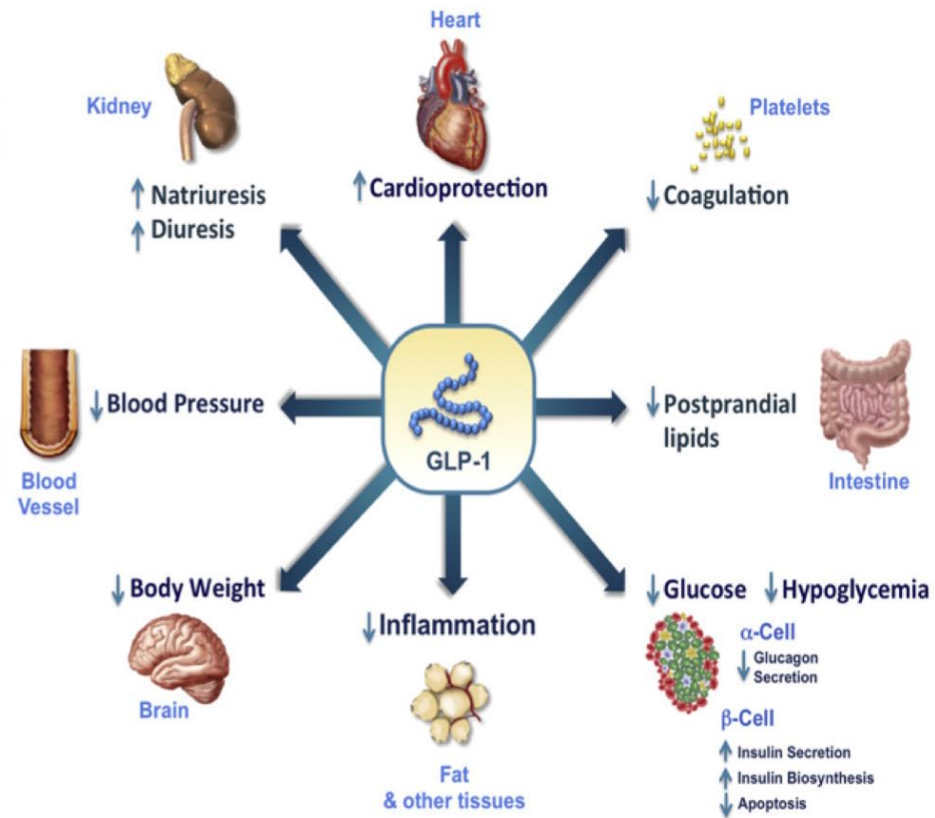
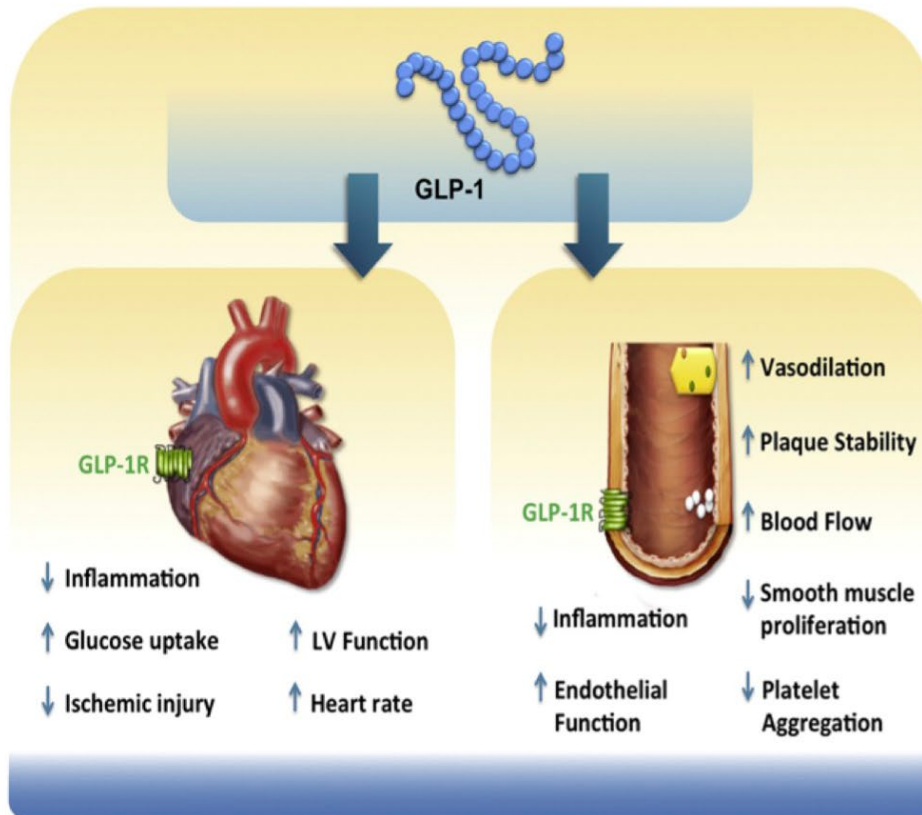
# Safety Profile of GLP1-RA



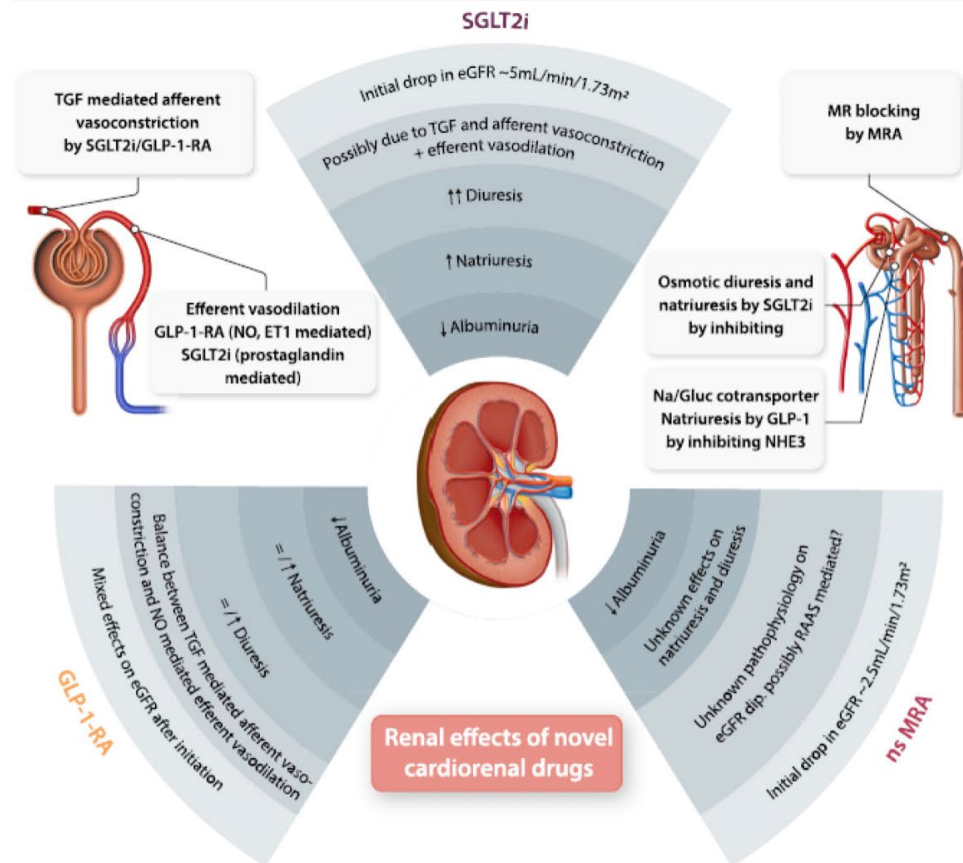
Gastrointestinal disorders: HR 1.63 (1.36-1.97)

Gallbladder disorders: HR 1.26 (1.12-1.41)

# GLP1-RA and **Cardiovascular** Protection Mechanisms



# Renal Protection Mechanisms of GLP1-RA



**Glomerular Hemodynamics:** modulate tubuloglomerular feedback and reduce intraglomerular pressure

**Tubular Effects:** inhibit NHE3 in proximal tubules

**Anti-inflammatory & Anti-fibrotic Action**

# Il rischio **cardiorrenale** ed aterosclerosi nel diabete tipo 2: un legame da non dimenticare

## Take Home Messages



### **Approccio farmacologico «olistico» al malato con sindrome cardio-nefro-metabolica:**

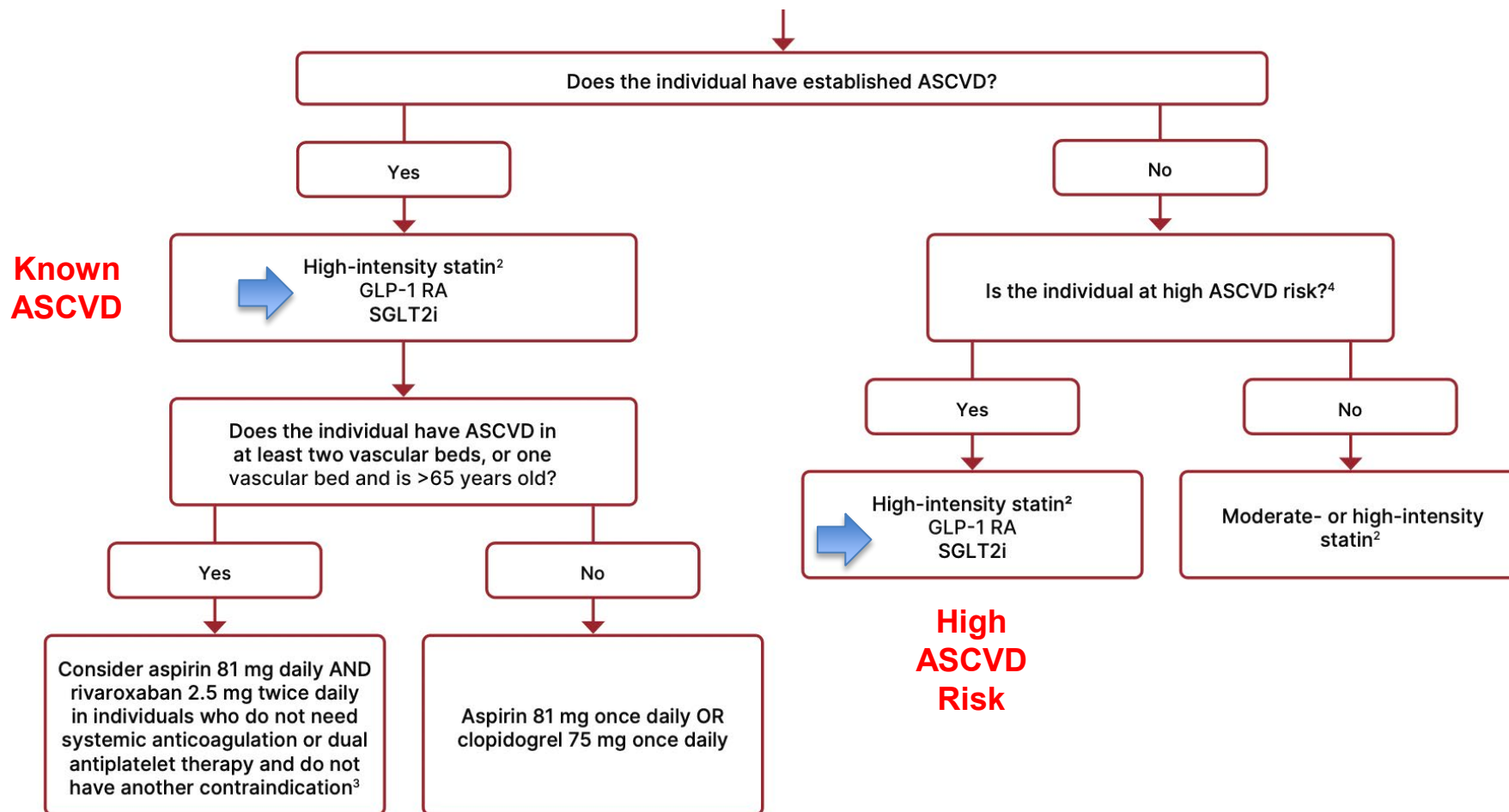
insieme composito di meccanismi patogenetici che determinano danno multisistemico



**GLP1 RA:** ↓ eventi avversi cardio-renali (+++ASCVD relati) e rappresentano un'opportunità terapeutica da mettere in campo precocemente per rallentare l'evoluzione del continuum cardio-renale

# Cardiovascular Disease and Risk Management: ADA Standards of Care in Diabetes—2026

Press Release 8 Dec 2026



Individuals at high risk for ASCVD include those with end-organ damage such as left ventricular hypertrophy or retinopathy or with multiple CV risk factors (e.g., older age, hypertension, smoking, dyslipidemia, CKD, and obesity).