Building Stepwise, Risk-Guided Intervention Strategies for ASCVD Primary Prevention

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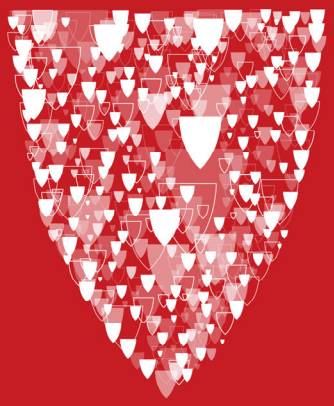
University Hospitals
Harrington Heart & Vascular Institute
Cleveland | Ohio



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Disclosures

Consulting, Advisory Board, and/or Speaker's Bureau:

- Boehringer Ingelheim
- Eli Lilly
- Bayer

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- NIH/NHLBI
- AHA
- The Peanut Institute
- American Pistachio Growers

Local site PI for industry sponsored trial:

- Amgen
- Novartis

Appointments

Associate Professor of Medicine, Case Western Reserve University School of Medicine

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1

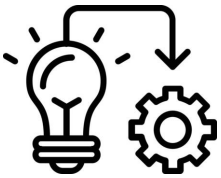
Who should receive stepwise/sequenced interventions?

2

What treatments should be sequenced?

3

How do we implement stepwise/sequenced interventions?



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Who should receive stepwise/sequenced interventions?

1. Initial CKM Staging
   - Stage 1
   - Stage 2-3
   - Stage 4

2. Risk Stratification using PREVENT and Risk Enhancers
   - PREVENT-CVD risk thresholds
   - + Risk Enhancers?

3. Patient Risk Profile with Specific CKM Conditions
   - Type 2 Diabetes
   - Chronic Kidney Disease
   - Obesity
   - Subclinical atherosclerosis or heart failure
   - Established ASCVD or heart failure

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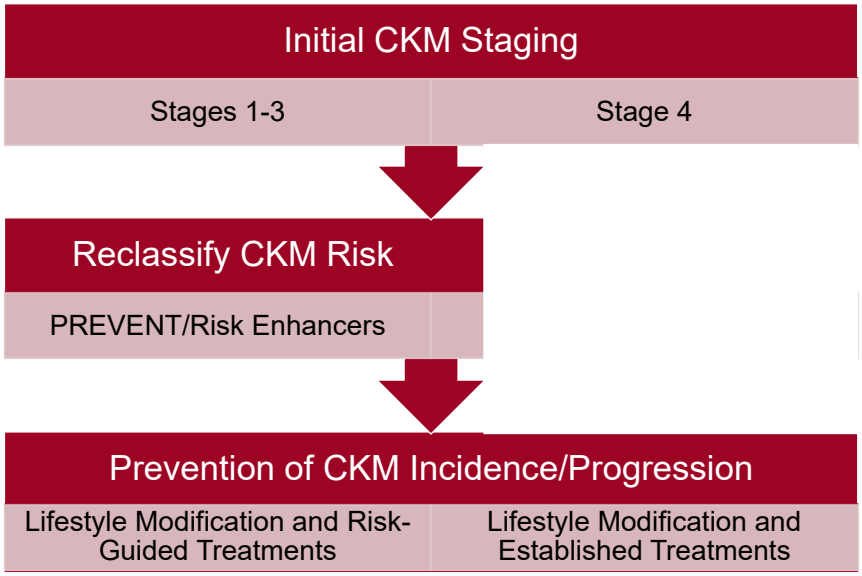

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What treatments should be sequenced?

1. Prioritize interventions with proven impact on CVD morbidity and mortality
2. Interventions with overlapping benefits
3. Complementary mechanisms of action
4. Current treatment during clinical trials
5. Subgroup analyses of clinical trials

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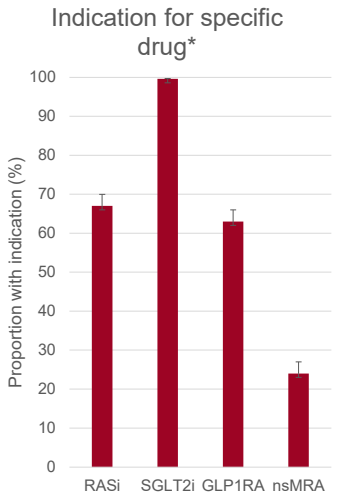
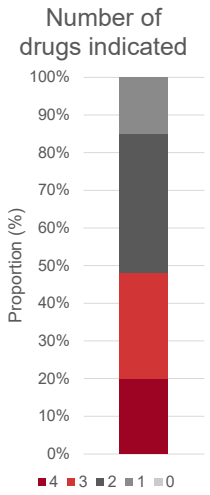
Therapies with overlapping benefits

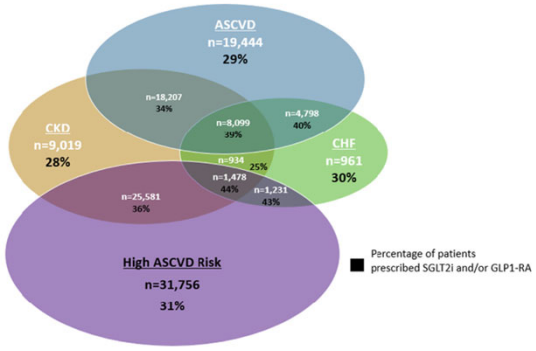




83% of 147,333 patients with T2D had an indication for SGLT2i +/- GLP1RA

Of these, 32% used at least one:

- 11% SGLT2i only
- 16% GLP1RA only
- 6% both



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Slide courtesy of Ian de Boer, MD
Unpublished data

Blood AJ et al. *Am Heart J*. 2025

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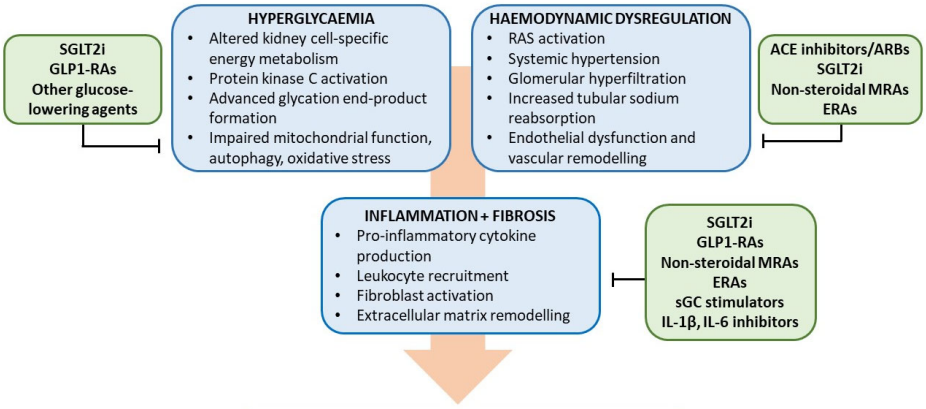
Current therapies have complimentary mechanisms of action



Slide courtesy of Ian de Boer, MD
Adapted from Sridhar VS et al. *Diabetologia*. 2024

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Concurrent treatment during clinical trials

Combination of therapies used during the FLOW trial

Characteristic	Semaglutide (N=1767)	Placebo (N=1766)	Total (N=3533)
Medication use — no. (%)			
SGLT2 inhibitor	277 (15.7)	273 (15.5)	550 (15.6)
ACE inhibitor	625 (35.4)	615 (34.8)	1240 (35.1)
ARB	1066 (60.3)	1061 (60.1)	2127 (60.2)
Lipid-lowering drug	1418 (80.2)	1416 (80.2)	2834 (80.2)
Diuretic agent	870 (49.2)	910 (51.5)	1780 (50.4)
Insulin	1083 (61.3)	1085 (61.4)	2168 (61.4)

Combination of therapies used during the SOUL trial

Cardiovascular-related medication at baseline — n (%)		
Lipid-lowering medication	4275 (88.6)	4297 (89.1)
Antiplatelet medication	3718 (77.1)	3727 (77.2)
Beta-blocker	3104 (64.3)	3097 (64.2)
Diuretic	2006 (41.6)	2058 (42.7)
ACE inhibitor	1990 (41.2)	1992 (41.3)
ARB	1814 (37.6)	1883 (39.0)
Calcium channel blocker	1762 (36.5)	1810 (37.5)
Anticoagulant medication	458 (9.5)	464 (9.6)
ARNI	17 (0.4)	18 (0.4)
Glucose-lowering medication at baseline — n (%)		
Metformin	3651 (75.7)	3675 (76.2)
Insulins	2476 (51.3)	2413 (50.0)
Sulfonylureas	1386 (28.7)	1434 (29.7)
SGLT2 inhibitors	1296 (26.9)	1300 (26.9)
DPP-4 inhibitors	1094 (22.7)	1141 (23.6)
Thiazolidinediones	225 (4.7)	188 (3.9)
α-glucosidase inhibitors	87 (1.8)	114 (2.4)
GLP-1 RAs and GIP GLP-1 RAs	0 (0.0)	2 (<0.1)
Other	70 (1.5)	53 (1.1)

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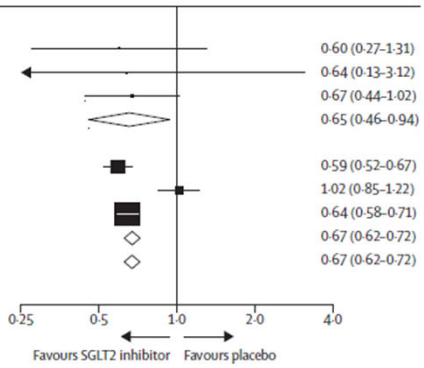
Subgroup analyses support combination therapy

SGLT2i + GLP-1 RA, SMART-C

	Events/patients (%)		Event rate per 100 patient years		HR (95% CI)
	SGLT2 inhibitor	Placebo	SGLT2 inhibitor	Placebo	
Baseline use of GLP-1 receptor agonist					
High atherosclerotic cardiovascular risk trials	14/936 (1·5%)	17/693 (2·5%)	0·4	1·0	0·60 (0·27–1·31)
Stable heart failure trials	3/47 (6·4%)	3/33 (9·1%)	2·2	4·7	0·64 (0·13–3·12)
Chronic kidney disease trials	40/635 (6·3%)	53/640 (8·3%)	3·2	4·5	0·67 (0·44–1·02)
Subtotal (I^2=0·0%, p=0·64)	57/1618 (3·5%)	73/1366 (5·3%)	1·6	2·8	0·65 (0·46–0·94)
No baseline use of GLP-1 receptor agonist					
High atherosclerotic cardiovascular risk trials	469/23585 (2·0%)	526/17302 (3·0%)	0·6	1·3	0·59 (0·52–0·67)
Stable heart failure trials	235/4781 (4·9%)	231/4798 (4·8%)	2·9	3·1	1·02 (0·85–1·22)
Chronic kidney disease trials	688/9839 (7·0%)	1015/9817 (10·3%)	3·7	5·6	0·64 (0·58–0·71)
Subtotal (I^2=70·4%, p<0·001)	1392/38205 (3·6%)	1772/31917 (5·6%)	1·7	2·9	0·67 (0·62–0·72)
Total	1449/39823 (3·6%)	1845/33283 (5·5%)	1·7	2·9	0·67 (0·62–0·72)
Heterogeneity by use of GLP-1 receptor agonist: p=0·81					



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Slide courtesy of Ian de Boer, MD

Apperloo EM et al. *Lancet Diabetes Endocrinol.* 2024

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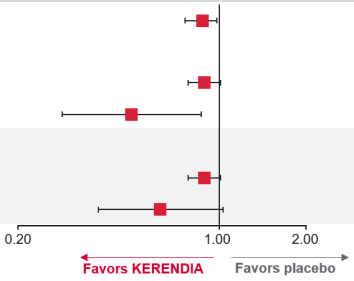
Subgroup analyses support combination therapy

SGLT2i or GLP-1 RA + ns-MRA

Exploratory analysis: FIGARO-DKD primary composite CV outcome in prespecified subgroups

Subgroup	KERENDIA	Placebo	KERENDIA	Placebo	HR (95% CI)
	No. of patients with event/ total no.		No. of patients with event per 100 PY		
All patients	**458/3686**	**519/3666**			**0.87 (0.76-0.98)**
SGLT2i at baseline					
No	434/3372	482/3362	4.01	4.50	0.89 (0.78-1.01)
Yes	24/314	37/304	2.37	3.95	0.49 (0.28-0.86)
GLP-1 RA at baseline					
No	427/3378	483/3424	3.96	4.44	0.89 (0.78-1.01)
Yes	31/308	36/242	2.97	4.69	0.62 (0.38-1.03)



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Pitt B et al. *N Engl J Med.* 2021

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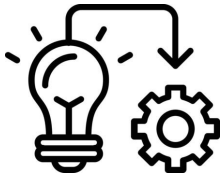
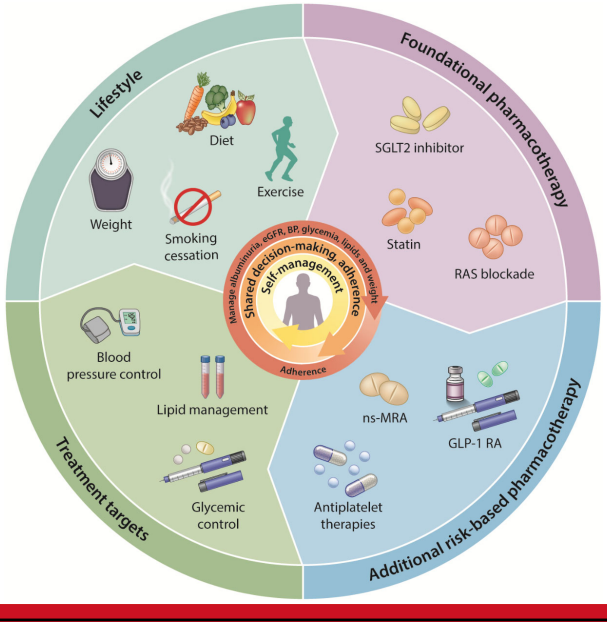
How do we implement stepwise/sequenced interventions?



EXAMPLE: 2026 KDIGO GUIDELINE



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How do we implement combination therapies?

Example: Chronic kidney disease

Combination Treatment Strategy	Advantages	Limitations
Sequential initiation Start and dose escalate ACEi or ARB → Start SGLT2 inhibitor if T2DM, heart failure, or albuminuria → Start nsMRA if still albuminuric with T2DM or heart failure / Start GLP-1 RA if needed for glycemic control	• Clear cause of adverse effects or intolerability • Avoidance of large eGFR dip after treatment initiation	• Long elapsed time between visits • Risk of therapeutic inertia • Increased lead time for initiating some treatments
Concomitant or rapid sequential initiation of multiple agents (CKM stage 4) Start indicated combination* of ACEi/ARB, SGLT2 inhibitor, nsMRA, and GLP-1 RA → Dose escalate as tolerated → Add additional agents as needed	• Avoids therapeutic inertia • Shortens lead time for initiating treatment	• Cost • Polypharmacy • Indicated in the setting of overt CVD • Potential for large drop in eGFR
Risk-based preventive combination treatment initiation (CKM stages 2-3) Risk stratify patients with PREVENT equations, KFRE, *etc.* → Start individualized preventive management with risk-based combination of treatments → Add additional agents as needed	• Individualized, risk-based preventive care • Starts treatment prior to the development of overt CVD	• **Knowledge gap:** Currently unclear how to best incorporate risk prediction models into clinical decision making

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Gregg LP et al. *CJASN*. 2025

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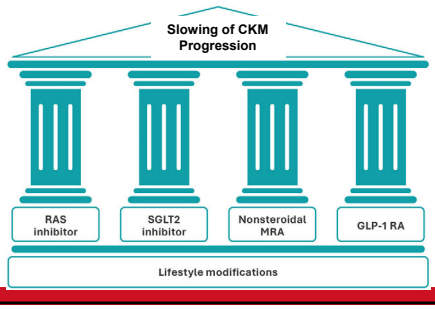
Suggested principles for risk-guided, sequential therapies

PERSONALIZED

- Underlying processes driving disease
- Absolute risks of CVD and kidney events
- Vulnerabilities to adverse drug effects/access



ACCELERATED

- Intervene early, at most amenable disease stages
- Rapid sequencing as tolerated

ITERATIVE

Reassess:

- Comorbidities
- Disease manifestations
- Residual risk
- Treatment indications
- Access to treatment
- Adherence

- Are the columns really the same width (strength of evidence)?
- Are the columns really the same height (effectiveness)?
- Will the temple collapse without all 4 (does everyone need all)?
- Should it be made of stone?

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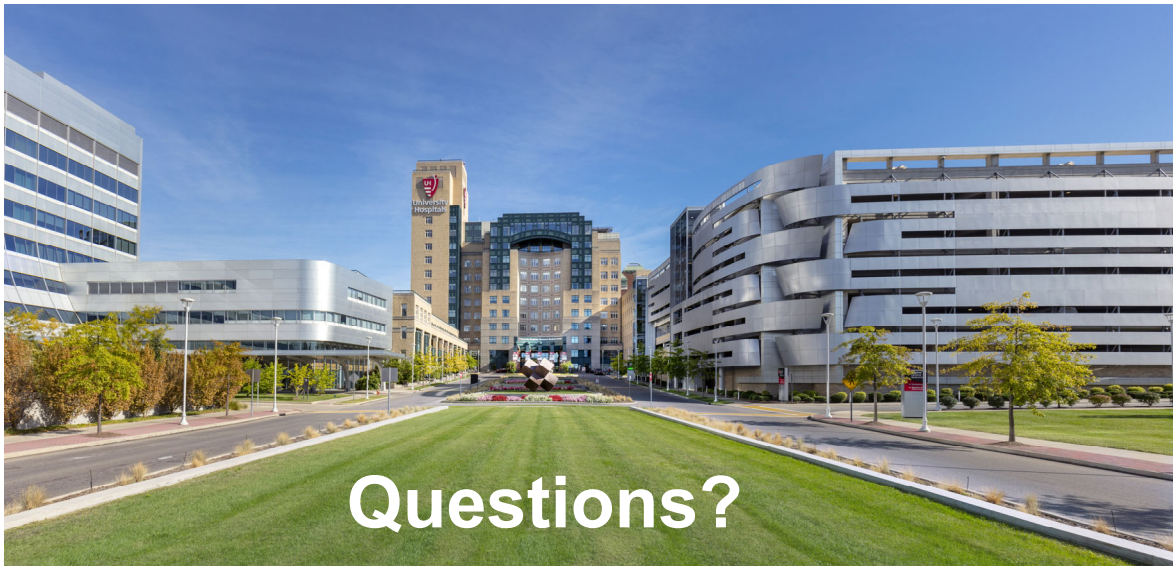

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