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DIABETES AND CVD MANAGEMENT:
TRANSLATING SCIENCE INTO PRACTICE

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CAUSES OF DEATH: USA (2017)

Rank	Cause	Number	Percent
	Total –all causes	2,813,503	100%
1	**Heart diseases**	647,457	23%
2	Cancer	599,108	21.3%
3	Accidents	169,936	6%
4	Chronic Lower Respiratory Disease	160,201	5.7%
5	**Stroke**	146,383	5.2%
6	Alzheimer's disease	121,404	4.3
7	**Diabetes mellitus**	83,564	3%
8	Influenza/pneumonia	55,672	2%
9	Kidney disease	50,633	1.8%
10	Suicide	47,173	1.7%

NCHS, National Vital Statistics System, Mortality.

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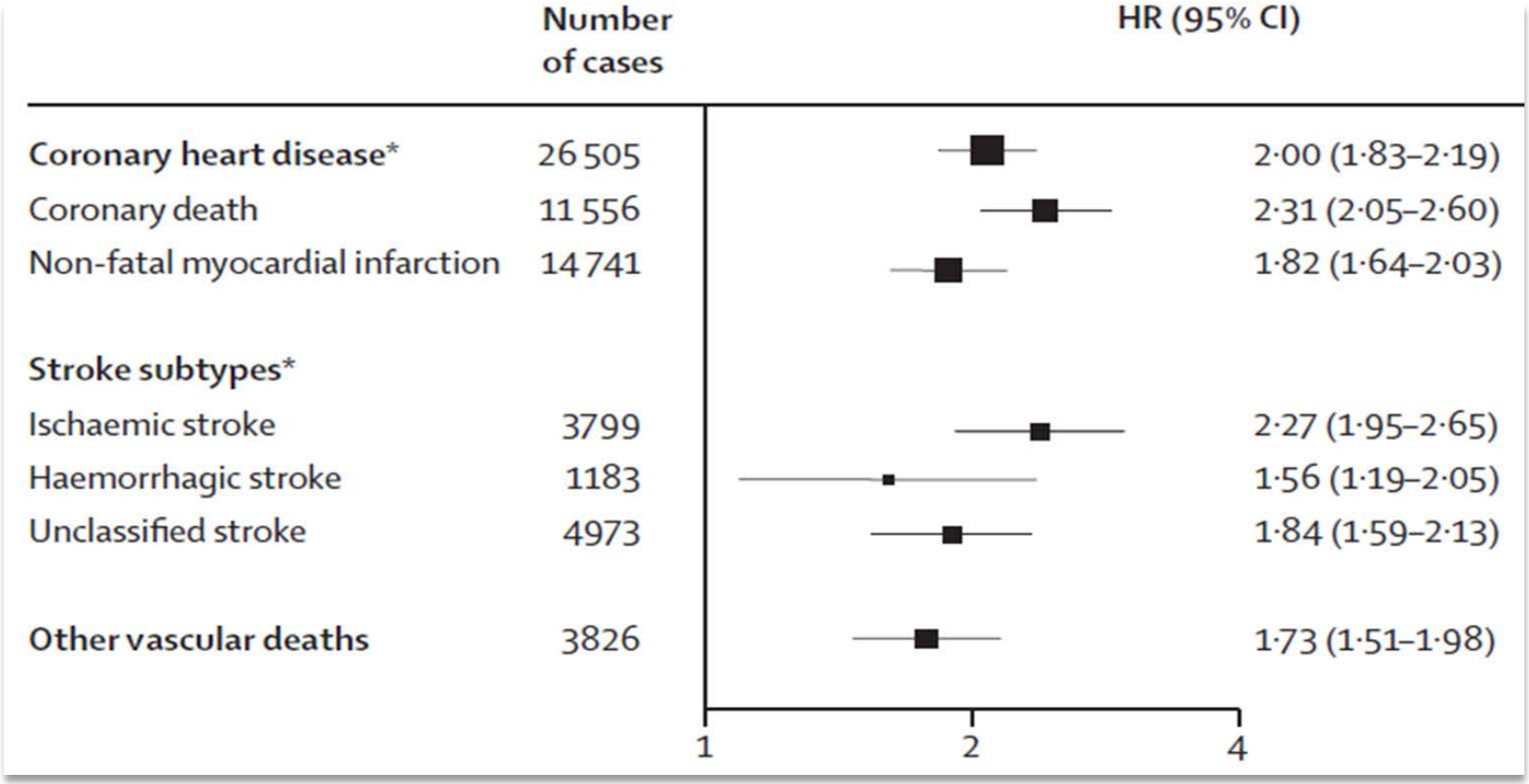
DIABETES & RISK OF MI & STROKE



Lancet 2010; 2215 (102 prospective studies, 700K people, 8.5M p-years f/u)

DEATHS ATTRIBUTABLE TO DIABETES IN THE U.S.

- The proportion of **deaths attributable to diabetes in 2010 was estimated to be 11.5% - 11.8%,** much greater than the 3.3–3.7% of deaths in which diabetes assigned as the underlying cause of death.
- Using proportion of deaths attributable to diabetes would make diabetes the **third leading cause of death in the United States**, after heart diseases and cancer.
- Including pre-diabetes, according to this approach, in the risk category would raise the proportion of deaths attributable to diabetes by an additional 2%.

Stokes A, Preston SH (2017) PLoS ONE 12(1): e0170219. https://doi.org/10.1371/journal.pone.0170219.

DIABETES: USA (2017)

AMONG US ADULTS WITH DIABETES

Smoking

- **15.9%** of adults were current smokers

Overweight and Obesity

- **61.3%** had obesity

Physical Inactivity

- **40.8%** (95% CI, 36.8%–45.0%) of adults were physically inactive, defined as getting less than 10 minutes a week of moderate or vigorous activity in each of the physical activity categories of work, leisure time, and transportation

Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services; 2017.

DIABETES: USA (2017)

AMONG US ADULTS WITH DIABETES

High Blood Pressure

- **73.6%** (95% CI, 69.9%–77.1%) of adults had systolic blood pressure of 140 mm Hg or higher or diastolic blood pressure of 90 mm Hg or higher, or they were on prescription medication for high blood pressure

High Cholesterol (Hyperlipidemia)

- **58.2%** of adults > 21 years or older with no self-reported cardiovascular disease but who were eligible for statin therapy were on a lipid-lowering medication – **31.8% were not**
- **66.9%** (95% CI, 58.5%–74.4%) of adults aged 21 years or older with self-reported cardiovascular disease who were thus eligible for statin therapy were on a lipid-lowering medication – **33.1% were not**

High Blood Glucose (Hyperglycemia)

- **15.6%** of adults had an A1C value higher than 9%.

Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services; 2017.

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2019 ACC/AHA GUIDELINE ON THE PRIMARY PREVENTION OF CVD

- **A team-based care approach** is an effective strategy for the prevention of cardiovascular disease.
- **Clinicians should evaluate social determinants of health** on individuals to inform treatment decisions.
- Adults who are at least age 40 and are being evaluated for CVD prevention **should undergo 10-year ASCVD risk estimation and have a clinician-patient risk discussion** before starting on pharmacologic therapy
- **Aspirin should infrequently be used in the routine primary prevention of ASCVD**

Arnett, D., Blumenthal, R., et al. Circulation, 2019.

2019 ACC/AHA GUIDELINE ON THE PRIMARY PREVENTION OF CVD

- **All adults should be assessed at every visit for tobacco use.**
- **All adults should consume a healthy diet** which emphasizes the intake of vegetables, fruits, nuts, whole grains, lean protein, and fish and minimizes the intake of trans fats, processed meats, refined carbohydrates, and sugar-sweetened beverages.
- **Adults should engage in at least 150 minutes per week of accumulated moderate intensity** or 75 minutes per week of vigorous intensity physical activity.

Arnett, D., Blumenthal, R., et al. Circulation, 2019.

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2019 ACC/AHA GUIDELINE ON THE PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE

- For adults who have been identified as overweight or obese, **counseling and caloric restriction are recommended** for achieving and maintaining weight loss
- **Nonpharmacological interventions are recommended for all adults with elevated blood pressure or hypertension.** For those requiring pharmacologic therapy, the target blood pressure should generally be less than 130/80 mm Hg.

Arnett, D., Blumenthal, R., et al. Circulation, 2019.

2019 ACC/AHA GUIDELINE ON THE PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE

- **Statin therapy is first-line treatment for primary ASCVD prevention in**:
  - Patients with elevated LDL-C levels (>190 mg/dl),
  - Those with diabetes, who are aged 40-75 years
  - Those at sufficient ASCVD risk following a clinician-patient risk discussion

- **For adults with type 2 diabetes mellitus, lifestyle changes such as improving dietary habits and achieving exercise recommendations are crucial.** If medication is indicated, metformin is first-line therapy followed by consideration of an SGLT-2 inhibitor or a GLP-1 receptor agonist.

Arnett, D., Blumenthal, R., et al. Circulation, 2019.

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COMPREHENSIVE CARDIOMETABOLIC HEALTH MANAGEMENT MODEL FOR PRIMARY CARE

ASCVD RISK CALCULATOR (10-Year & Lifetime Risk)

- Age, sex, race
- Measure blood pressure (systolic blood pressure)
- Measure lipid levels (total cholesterol, HDL cholesterol)
- Blood pressure lowering medication use
- Determine diabetes status
- Assess tobacco use (smoking status)

https://professional.heart.org/professional/GuidelinesStatements/ASCVDRiskCalculator/UCM_457698_ASCVD-Risk-Calculator.jsp

COMPREHENSIVE CARDIOMETABOLIC HEALTH MANAGEMENT MODEL FOR PERSONS WITH T2DM

LIFE'S SIMPLE 7 ASSESSMENT

1. Measure height, weight, waist circumference
2. Measure blood pressure
3. Measure A1C
4. Measure lipid levels (total cholesterol, HDL)
5. Assess tobacco use
6. Assess physical activity level
7. Assess dietary pattern

Benjamin et al; Circulation 2017

MORTALITY & CVD DISEASE IN TYPE 1 & TYPE 2 DIABETES

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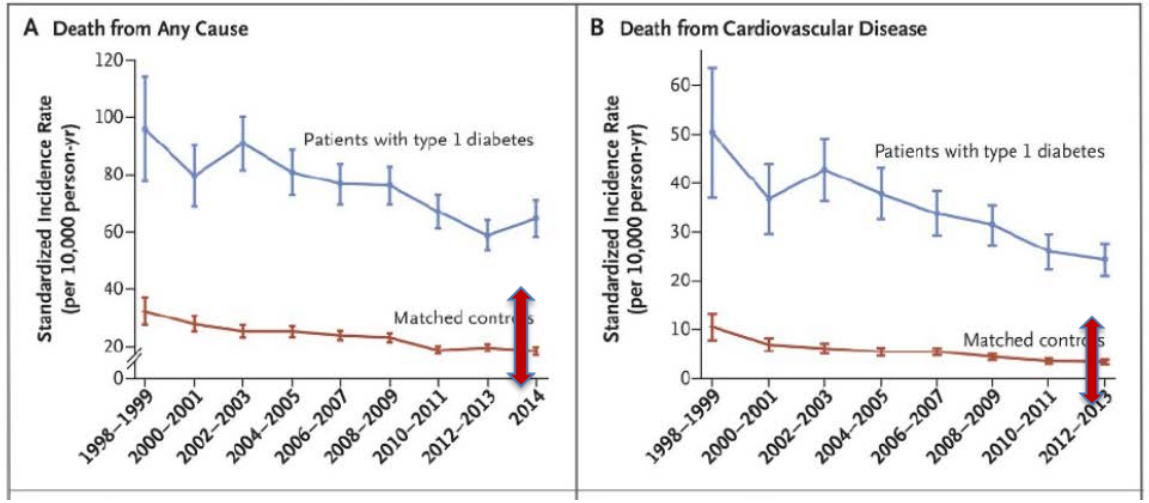
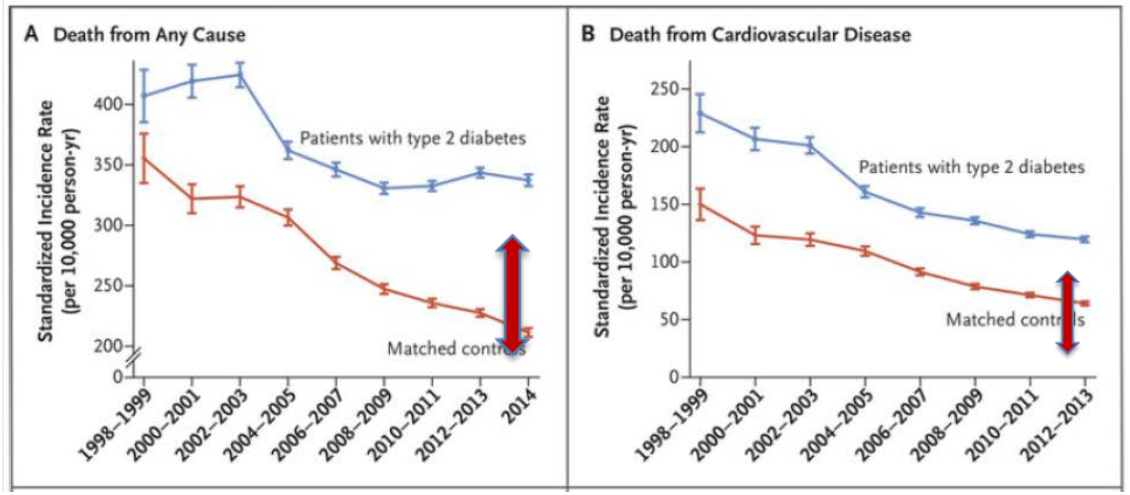
Patients with Type 1 DM



Patients with Type 2 DM



"…data from 1998 to 2014 showed marked reductions in mortality and in the incidence of cardiovascular complications among adults with either type 1 diabetes or type 2 diabetes".

"Residual Risk"

"There remains a substantial excess overall rate of all outcomes analyzed among persons with either type 1 diabetes or type 2 diabetes as compared with the general population.

Rawshani A, Franzen S et al. N Engl J Med. 2017 April 13;376 (15):1407-1418

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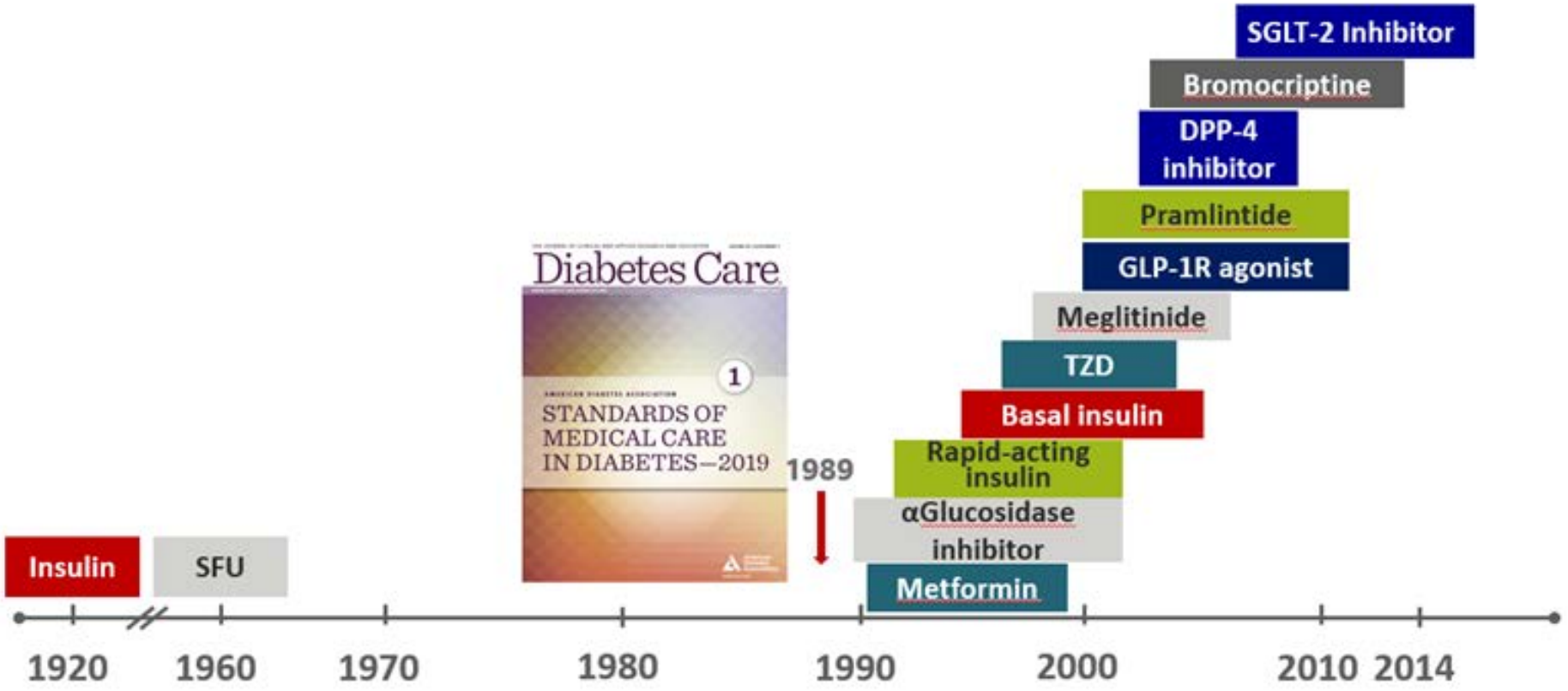
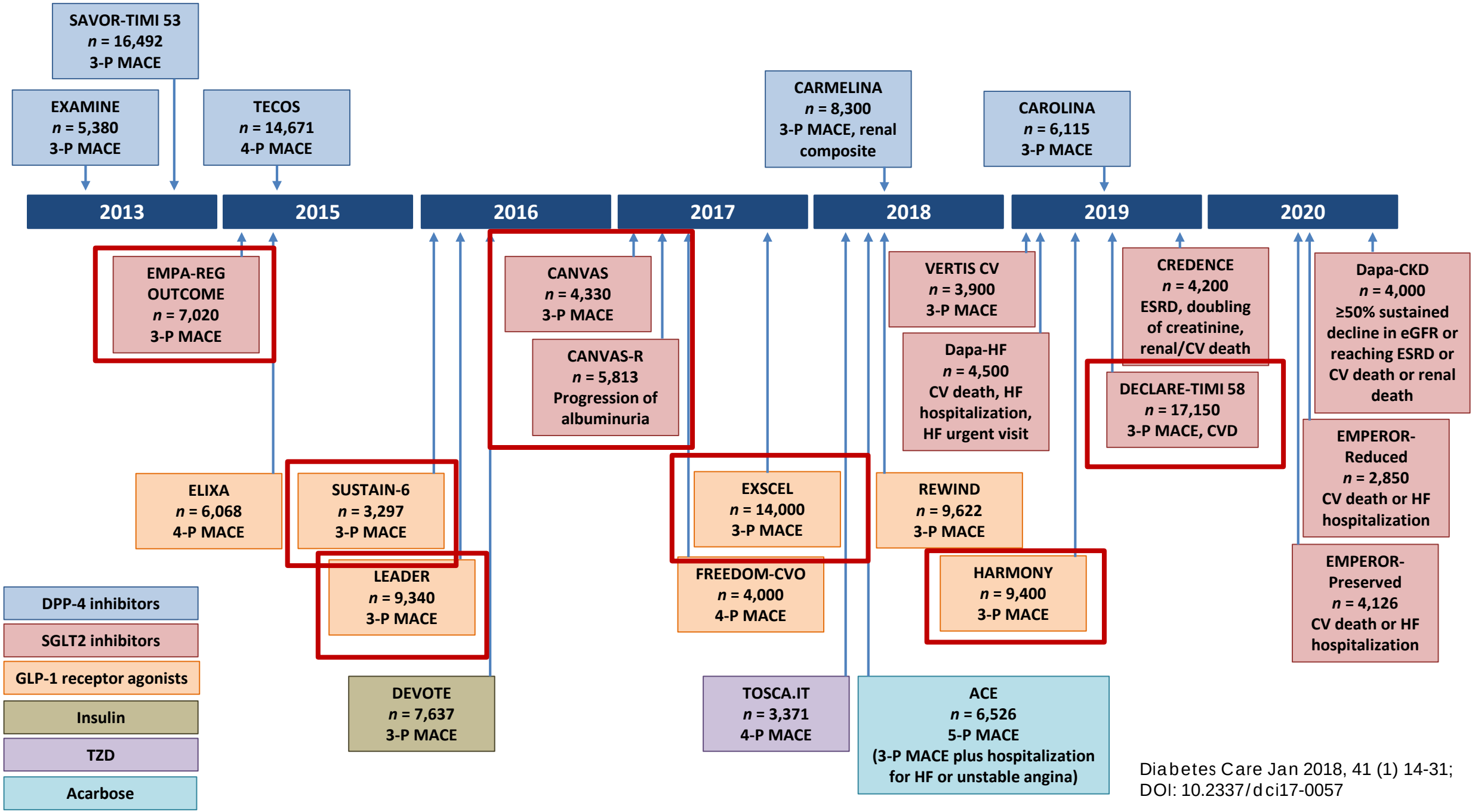
THERAPEUTIC ADVANCES OVER PAST 20 YEARS



Diabetes Care Jan 2018, 41 (1) 14-31; DOI: 10.2337/dci17-0057



Diabetes Care Jan 2018, 41 (1) 14-31;
DOI: 10.2337/dci17-0057

GLP1RA CVOTS: META-ANALYSIS

3 Point MACE

Mortality

	GLP-1 receptor agonist	Placebo	Hazard ratio (95% CI)	p value
ELIXA	400/3034 (13%)	392/3034 (13%)	1·02 (0·89–1·17)	0·776
LEADER	608/4668 (13%)	694/4672 (15%)	0·87 (0·78–0·97)	0·015
SUSTAIN 6	108/1648 (7%)	146/1649 (9%)	0·74 (0·58–0·95)	0·016
EXSCEL	839/7356 (11%)	905/7396 (12%)	0·91 (0·83–1·00)	0·061
Overall			**0·90 (0·82–0·99)**	**0·033**
Test for heterogeneity: p=0·11, I^2=50%				
ELIXA	211/3034 (7%)	223/3034 (7%)	0·94 (0·78–1·13)	0·50
LEADER	381/4668 (8%)	447/4672 (10%)	0·85 (0·74–0·97)	0·020
SUSTAIN 6	62/1648 (4%)	60/1649 (4%)	1·05 (0·74–1·50)	0·79
EXSCEL	507/7356 (7%)	584/7396 (8%)	0·86 (0·77–0·97)	0·016*
Overall			**0·88 (0·81–0·95)**	**0·002**
Test for heterogeneity: p=0·63, I^2=0%				

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Bethel et al. Lancet 2018; 6:105

SGLT2I CVOTS: META-ANALYSIS

Q statistic = 1·20, p=0·55, I^2= 0%

Bethel et al. Lancet 2018; 6:105

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PUTTING THE PATIENT AT THE CENTRE OF CARE

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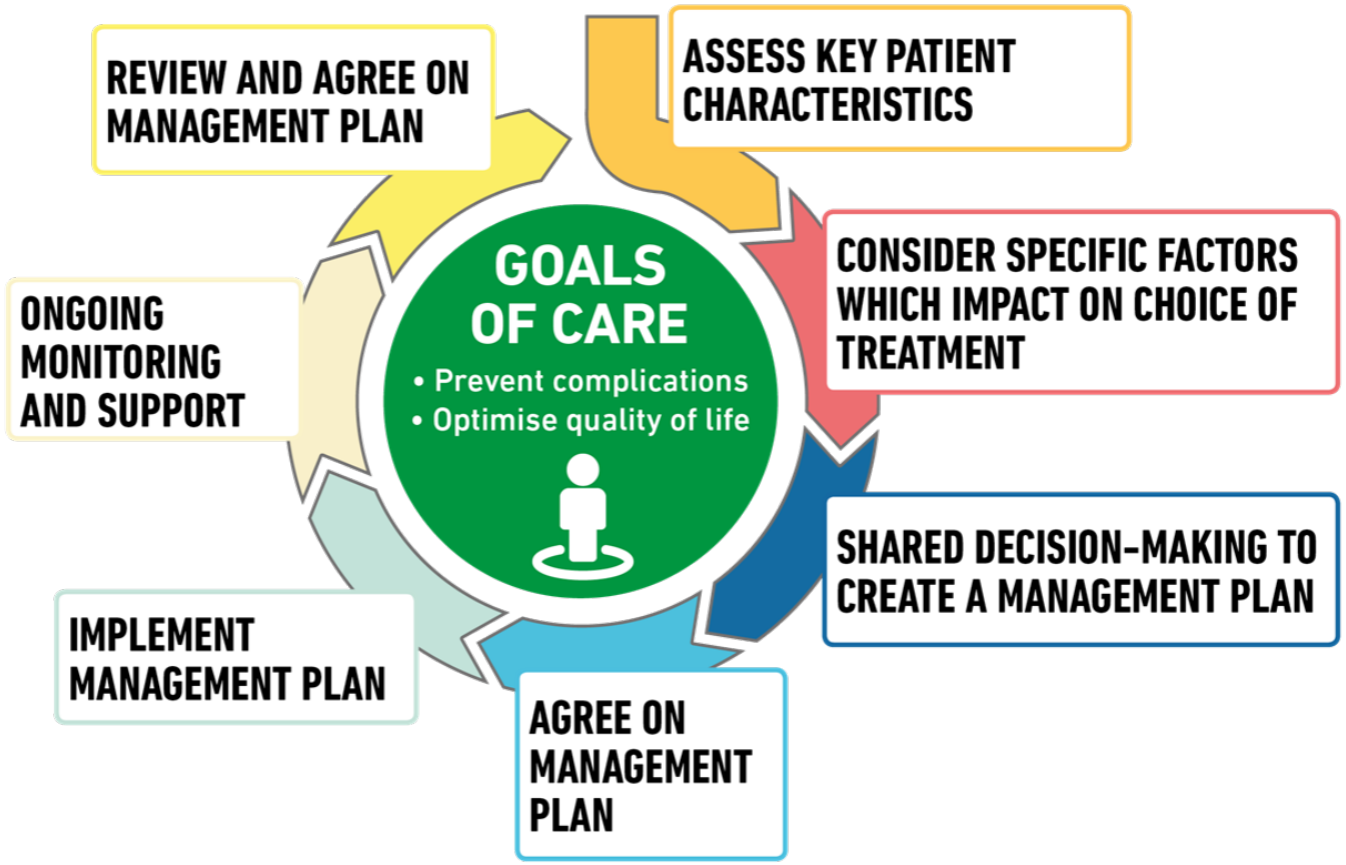
DECISION CYCLE FOR PATIENT-CENTRED GLYCAEMIC MANAGEMENT IN TYPE 2 DIABETES



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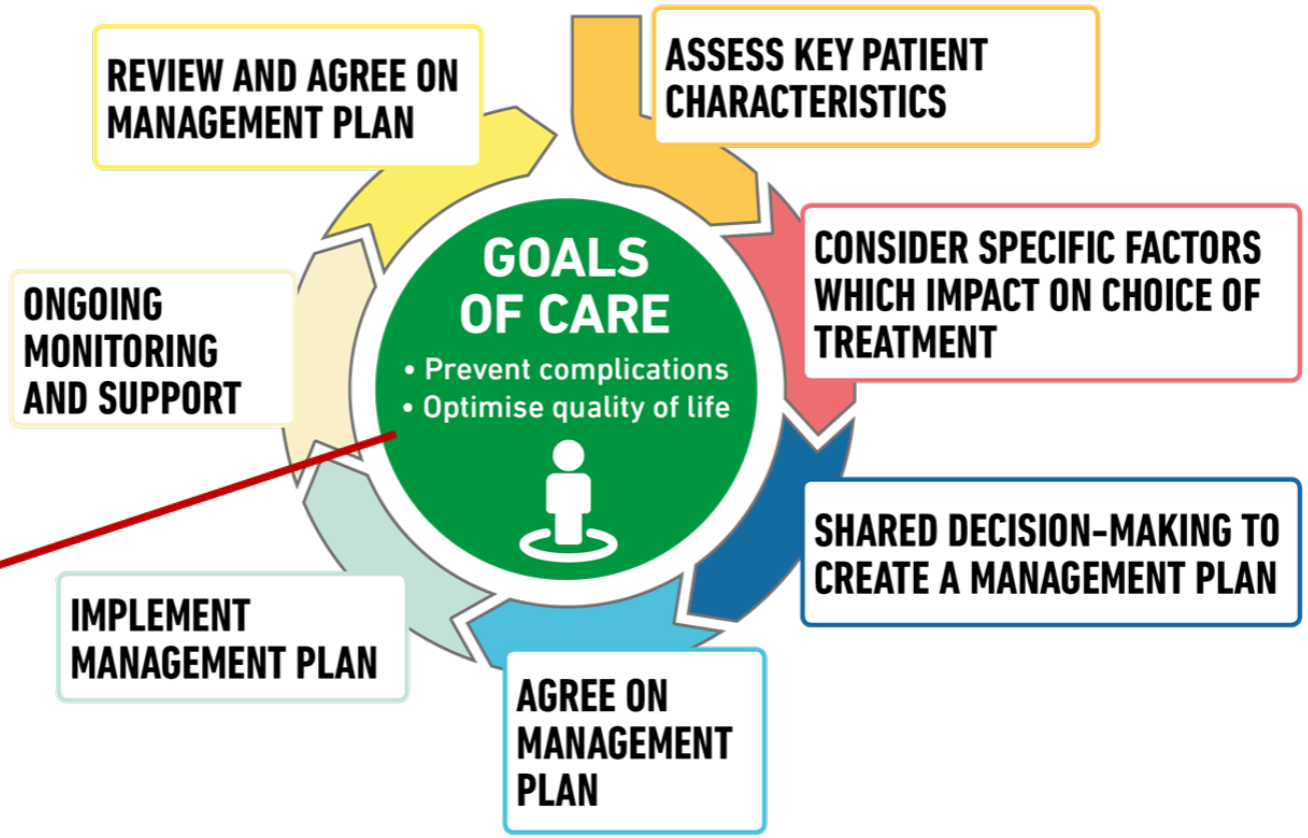
DECISION CYCLE FOR PATIENT-CENTRED GLYCAEMIC MANAGEMENT IN TYPE 2 DIABETES



"Optimize quality of life"

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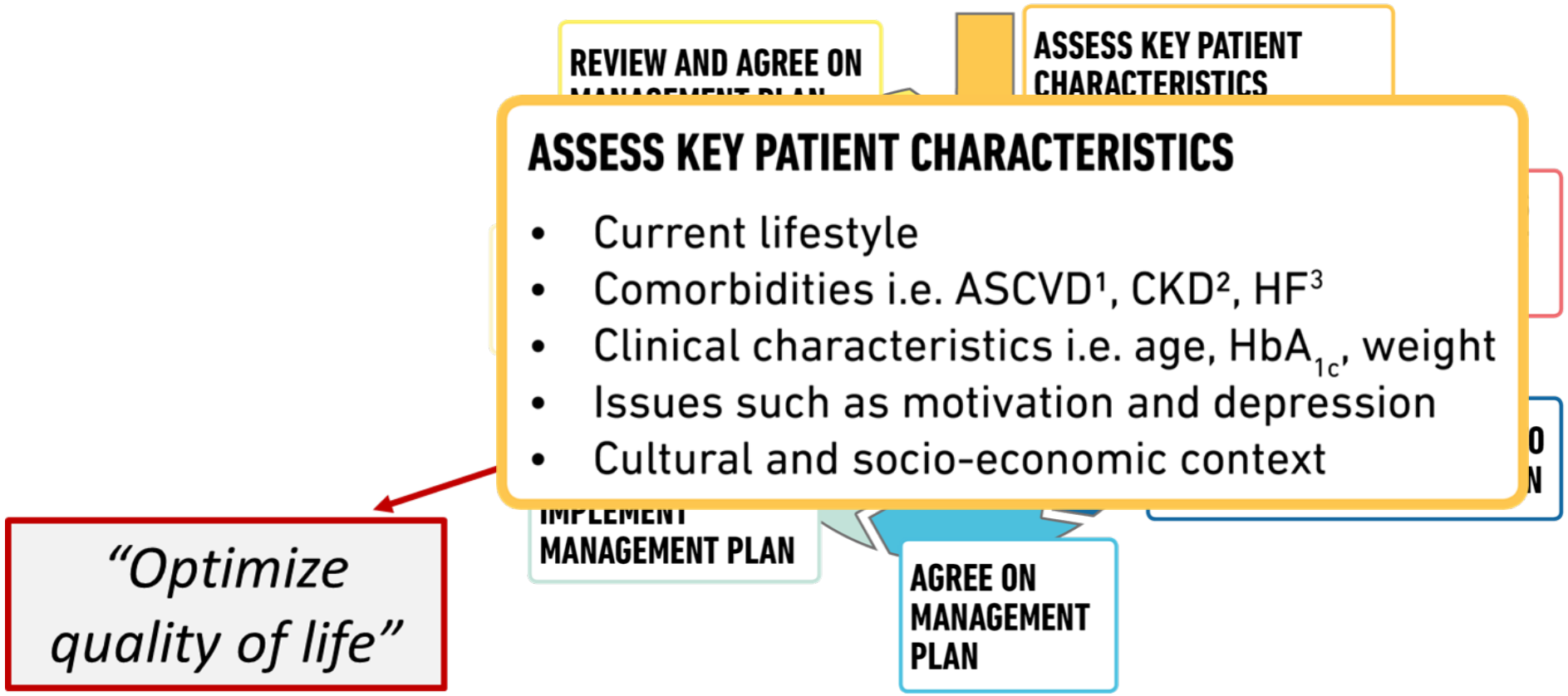

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STEP 1:
ASSESS CARDIOVASCULAR DISEASE

PRESENCE OF CARDIOVASCULAR DISEASE IS COMPELLING INDICATION

ASCVD predominates

HF or CKD predominates

Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41:2669–2701

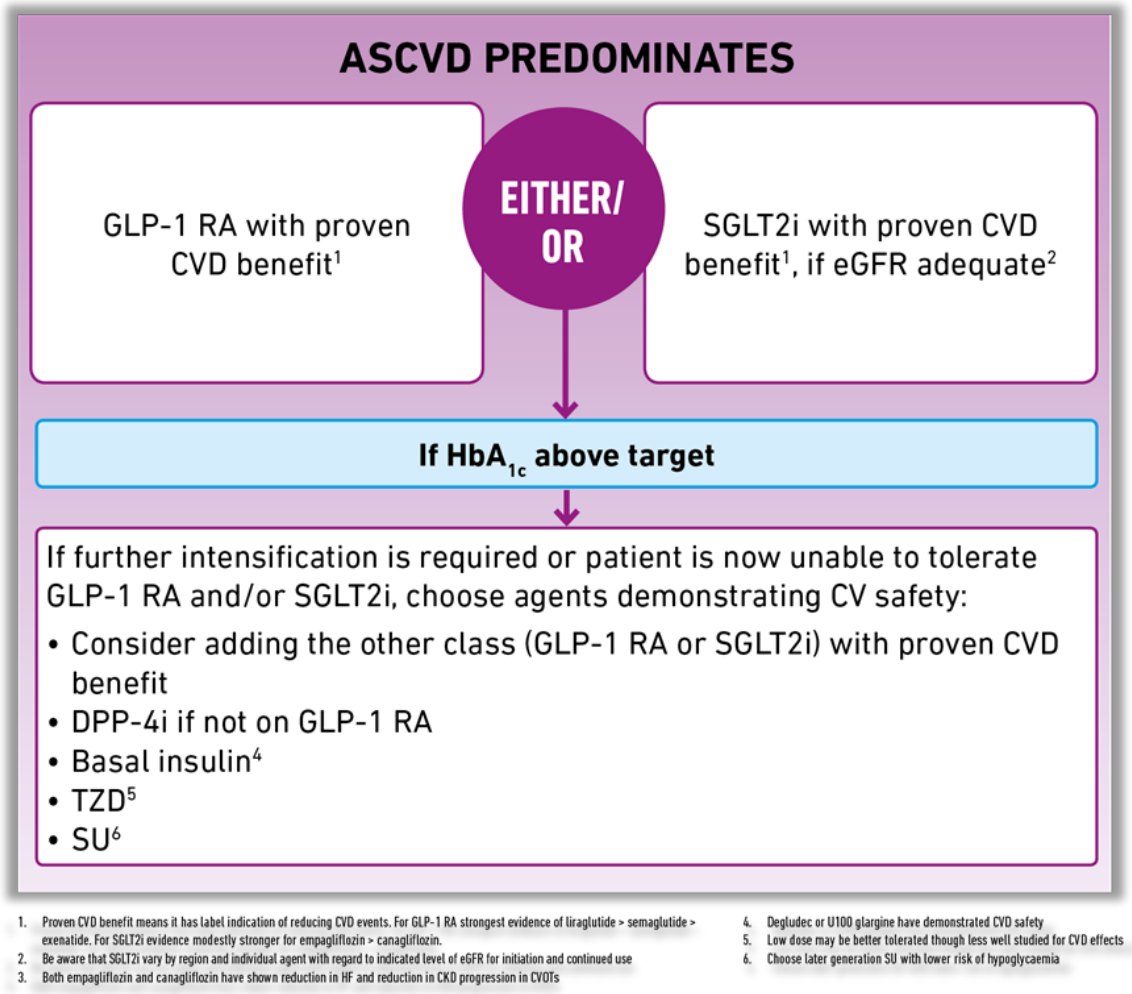
IF ASCVD PREDOMINATES

GLP-1 receptor agonist with proven *cardiovascular benefit*

- Liraglutide > semaglutide > exenatide LAR

SGLT2 inhibitor with proven cardiovascular benefit

- Empagliflozin > canagliflozin



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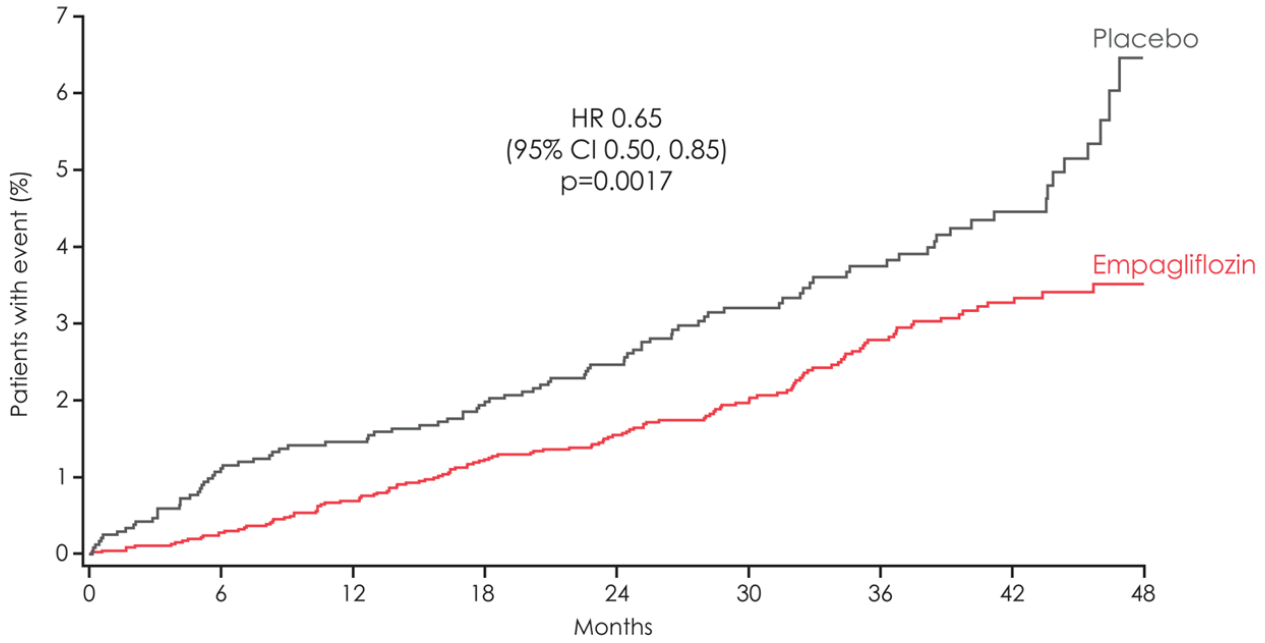
DIABETES & RISK OF HEART FAILURE, HOSP/DEATH

MacDonald et al. Eur Heart J 2008;29:1377-85

EMPA-REG

HOSPITALIZATION FOR HEART FAILURE, SECONDARY OUTCOME



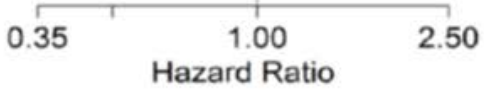
No. of patients									
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

Cumulative incidence function. HR, hazard ratio

Zinman et al. N Engl J Med 2015;373:2117–28

SGLT2I CVOTS: META-ANALYSIS – CV OUTCOMES

Heart Failure Hospitalization	Patients	Events	Treatment Events per 1000 pt-yrs	Placebo Events per 1000 pt-yrs	Weights (%)	HR [95% CI]
EMPA-REG OUTCOME	7020	221	9.4	14.5	24.0	0.65 [0.50, 0.85]
CANVAS Program	10142	243	5.5	8.7	25.6	0.67 [0.52, 0.87]
DECLARE-TIMI 58	17160	498	6.2	8.5	50.4	0.73 [0.61, 0.88]
FE Model (P-value <0.0001)						**0.69 [0.61, 0.79]**



Q statistic = 0·60, p=0·74, I^2= 0%

Zelniker et al. Lancet 2018; Online

SGLT2I CVOTS: META-ANALYSIS: ROLE OF EGFR

eGFR	Renal Fⁿ, ESRD or Renal Death	Heart Failure Hospitalization	MI, Stroke, or CV Death
<60	0.67 (051, 0.89)	0.60 (0.47, 0.77)	0.82 (0.70, 0.95)
60-89	0.56 (0.46, 0.70)	0.69 (0.57, 0.83)	0.91 (0.82, 1.00)
> 90	0.44 (0,32, 0,59)	0.88 (0,68, 1.13)	0.94 (0.82, 1.07)
P Trend	0.026	0.007	0.2
As eGFR Falls…	Less effective	More effective	More effective

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Zelniker et al. Lancet 2018; Online

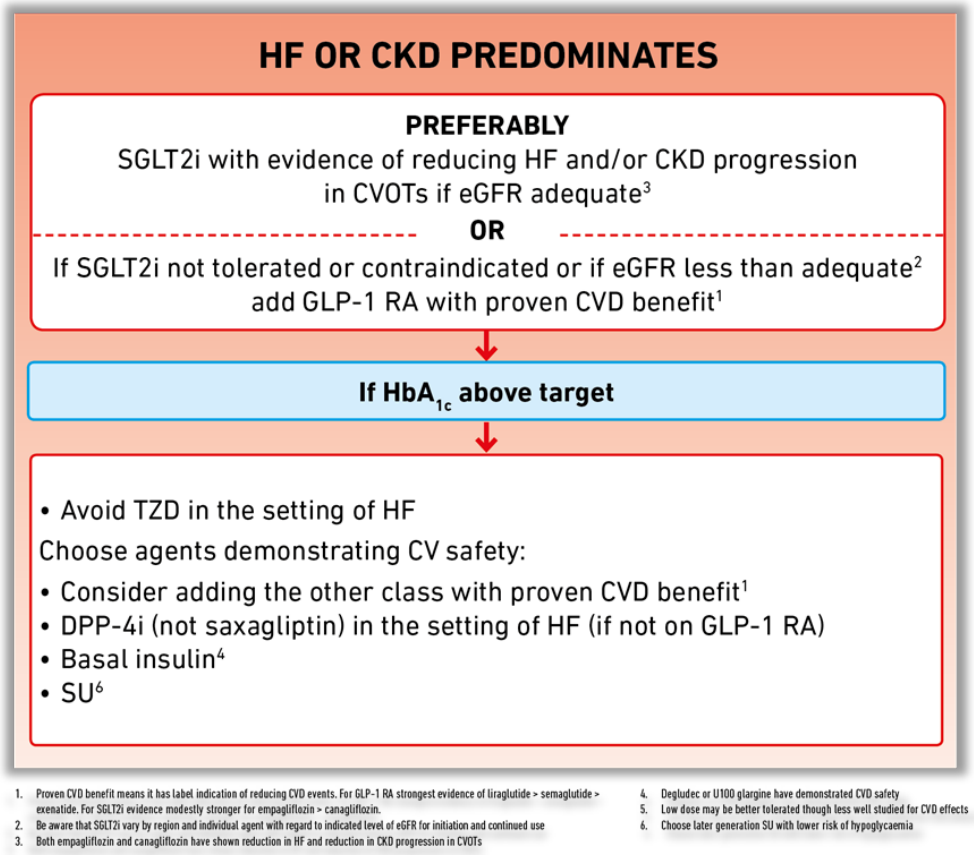
AMONG PATIENTS WITH ASCVD IN WHOM HF COEXISTS OR IS OF CONCERN, SGLT2 INHIBITOR ARE RECOMMENDED

RATIONALE

- Patients with T2D are at increased risk for heart failure with reduced or preserved ejection fraction
- Significant, consistent reductions in hospitalization for heart failure have been seen in SGLT2 inhibitor trials

CAVEAT

- Trials were not designed to adjudicate heart failure
- Majority of patients did not have clinical heart failure at baseline



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CONSIDERATIONS FOR THERAPY: HF AND CKD

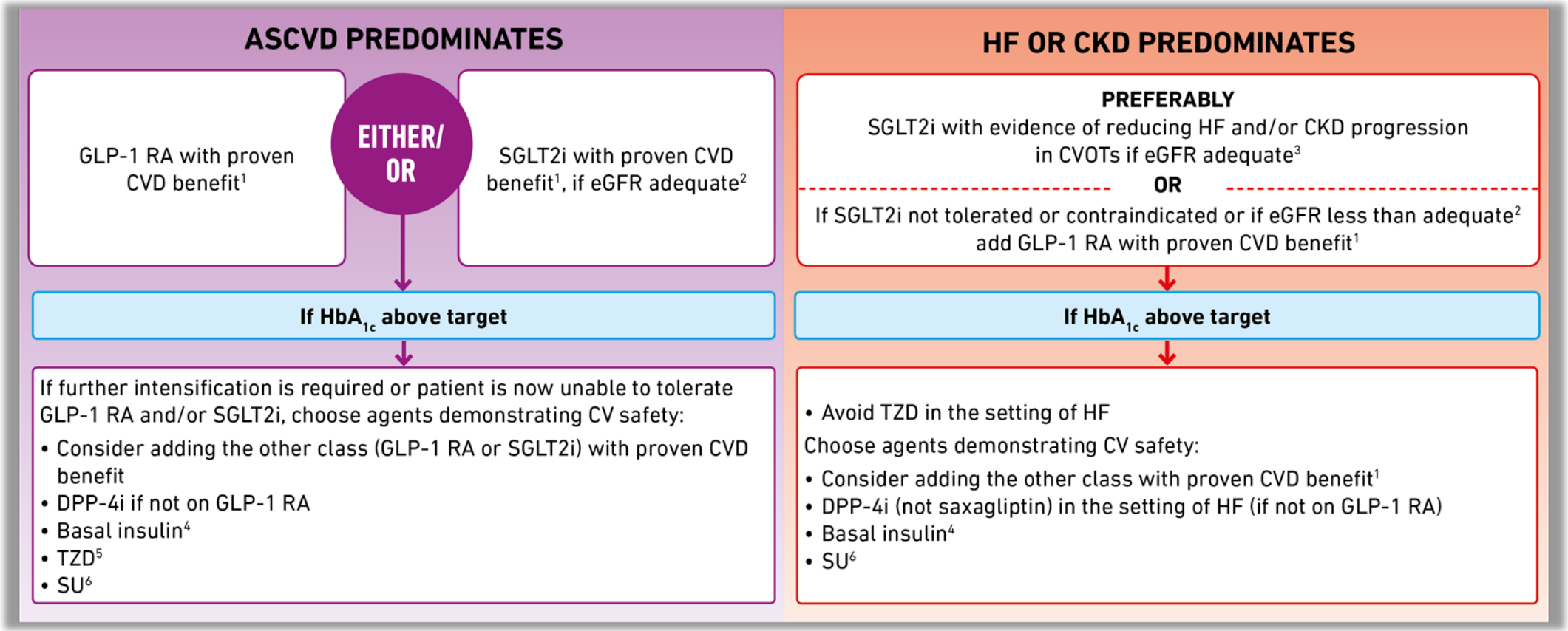
HEART FAILURE: hospitalization for heart failure was reduced consistently with SGLT2-i in two trials but was a secondary outcome

CHRONIC KIDNEY DISEASE: for patients with type 2 diabetes **and** CKD, with or without cardiovascular disease, consider the use of an SGLT2 inhibitor shown to reduce CKD progression or…….if contraindicated or not preferred, a GLP-1 receptor agonist shown to reduce CKD progression

CONSIDERATIONS FOR THERAPY: HF AND CKD

- For SGLT2-i adequate eGFR differs between countries and compounds
- SGLT2-i are registered as glucose-lowering agents to be started if eGFR>45-60 ml/min/1.73m2 and stopped at eGFR 45-60, as glucose-lowering effect declines with eGFR
- SGLT2-i CVOTS included patients with eGFR>30, and there were no excess adverse events in subjects with eGFR<60
- for GLP-1 RA gastrointestinal side effects increase with declining renal function are not recommended in end stage renal disease due to limited experience

CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ASCVD OR CKD



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence of liraglutide > semaglutide > exenatide. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycaemia

Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41:2669–2701

SUMMARIZING THE APPROACH TO MANAGEMENT

BALANCING **RISKS** AND **BENEFITS** FOR PERSONALIZED GOALS

MORE STRINGENT CONTROL

- No hypoglycemia
- Less complexity/polypharmacy
- Lifestyle or metformin only
- Short disease duration
- Long life expectancy
- No CVD

LESS STRINGENT CONTROL

- History of severe hypoglycemia
- High burden of therapy
- Longer disease duration
- Limited life expectancy
- Extensive co-morbidity
- CVD

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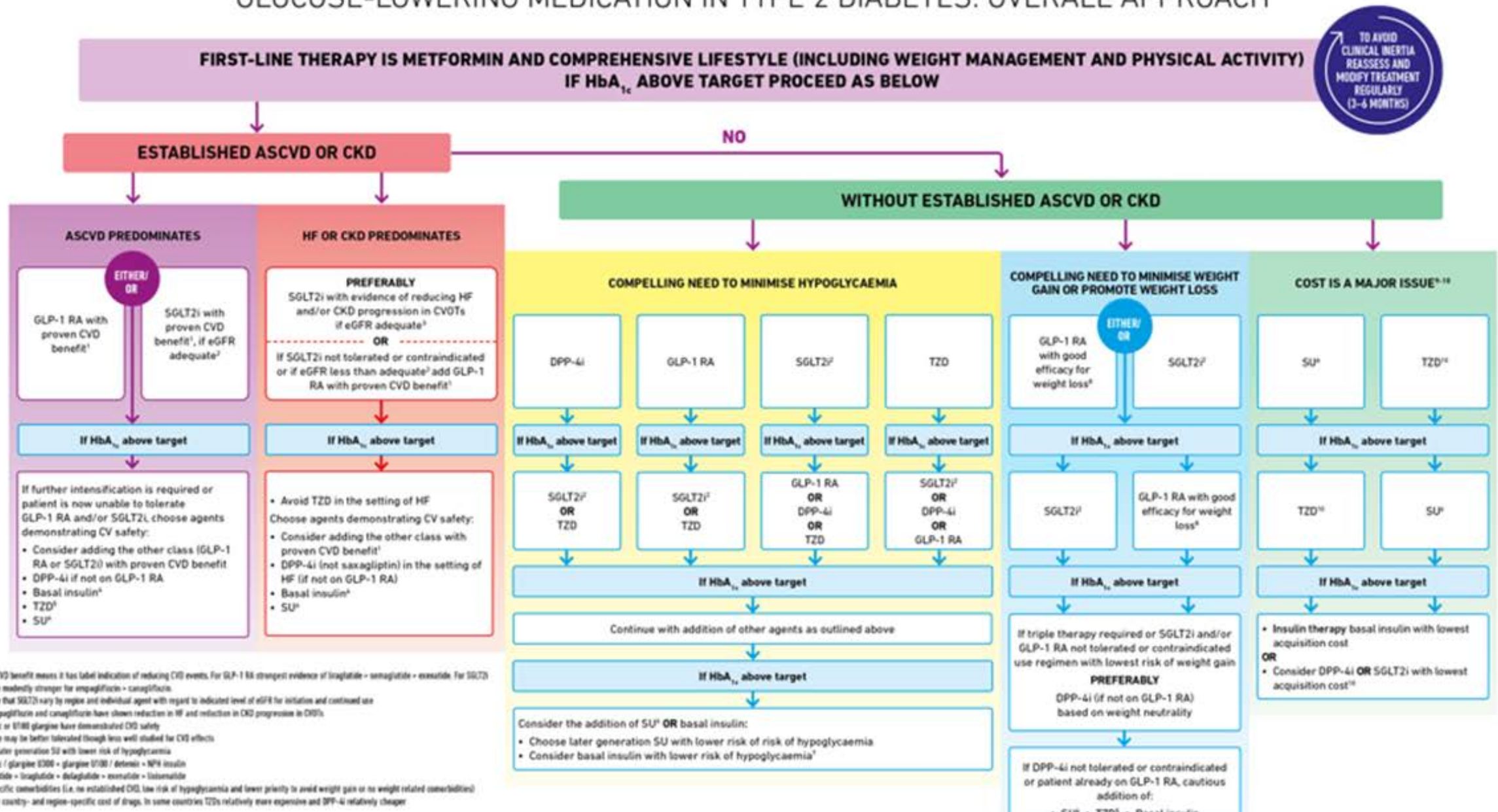
GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



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7. Degludec / glargine U300 > glargine U100 / detemir > NPH insulin.
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide.
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight related comorbidities).
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper.

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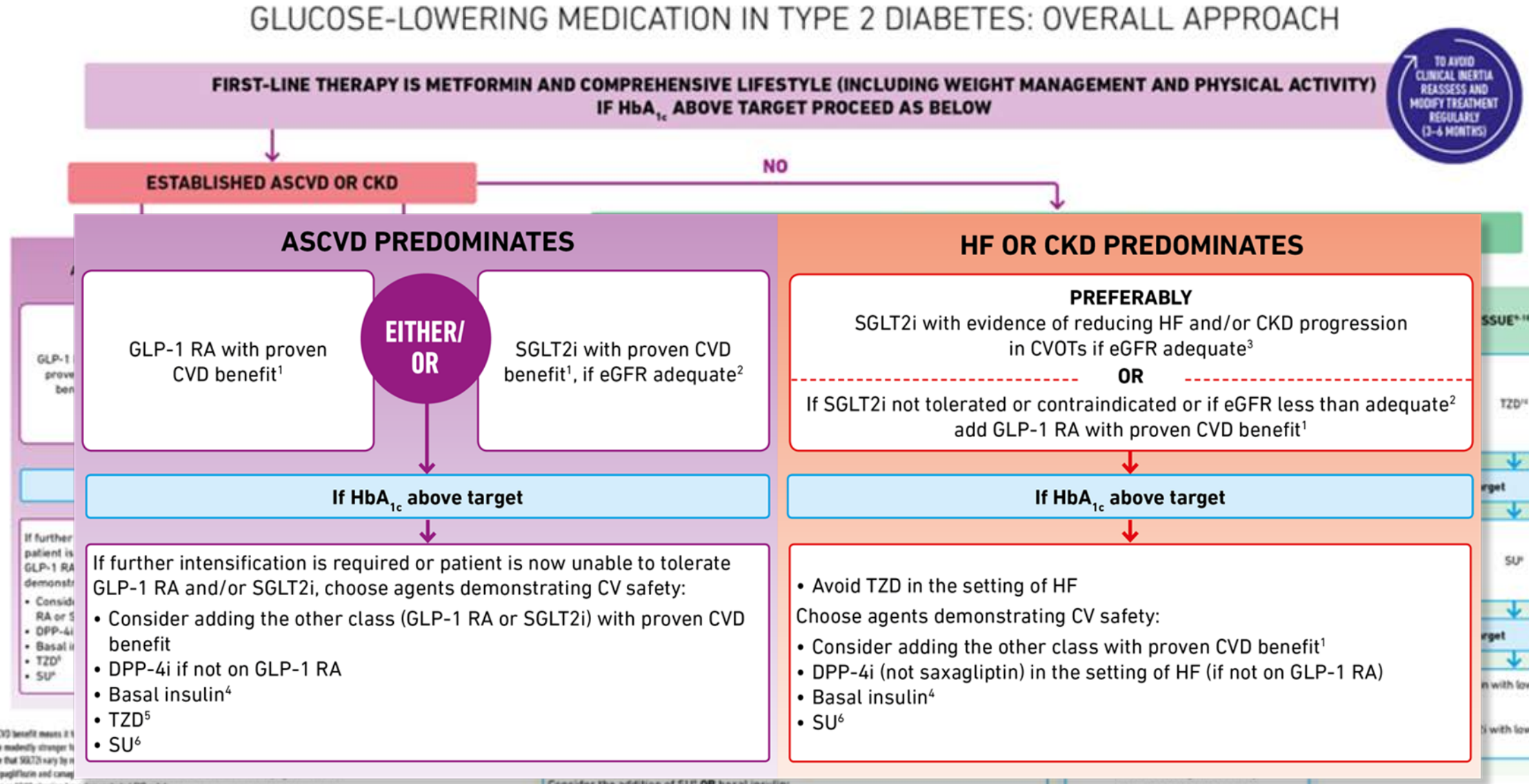

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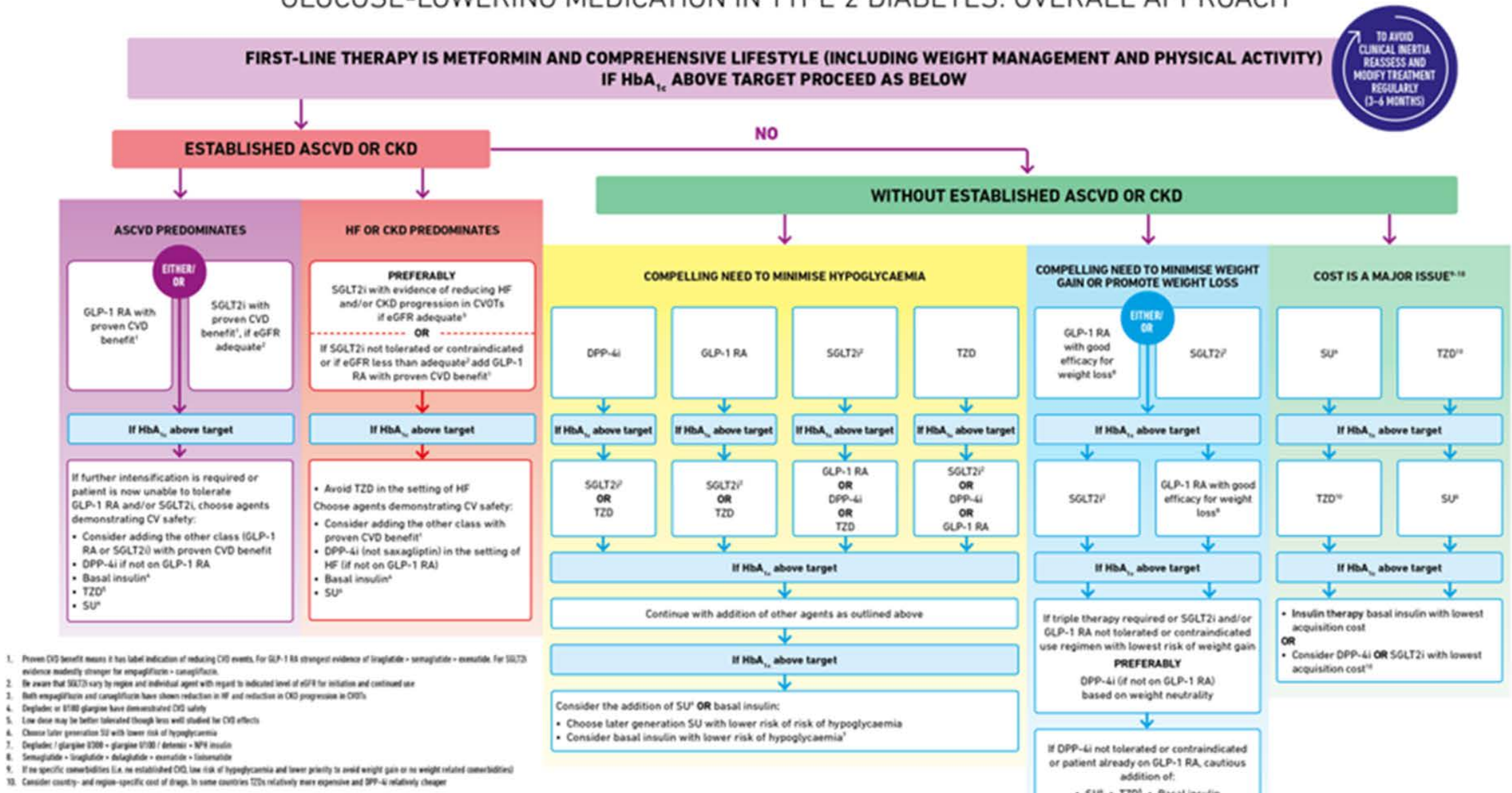
GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



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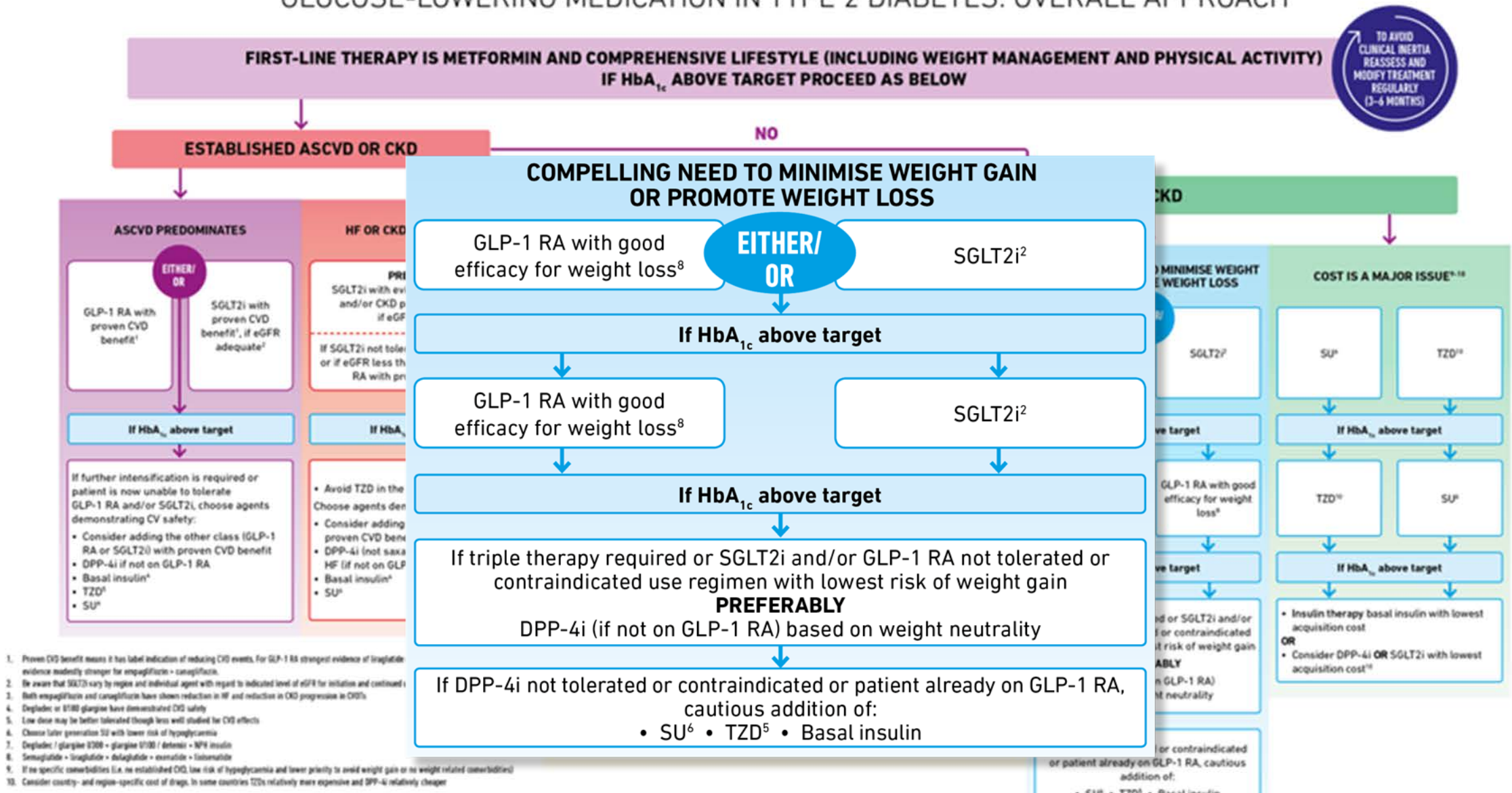

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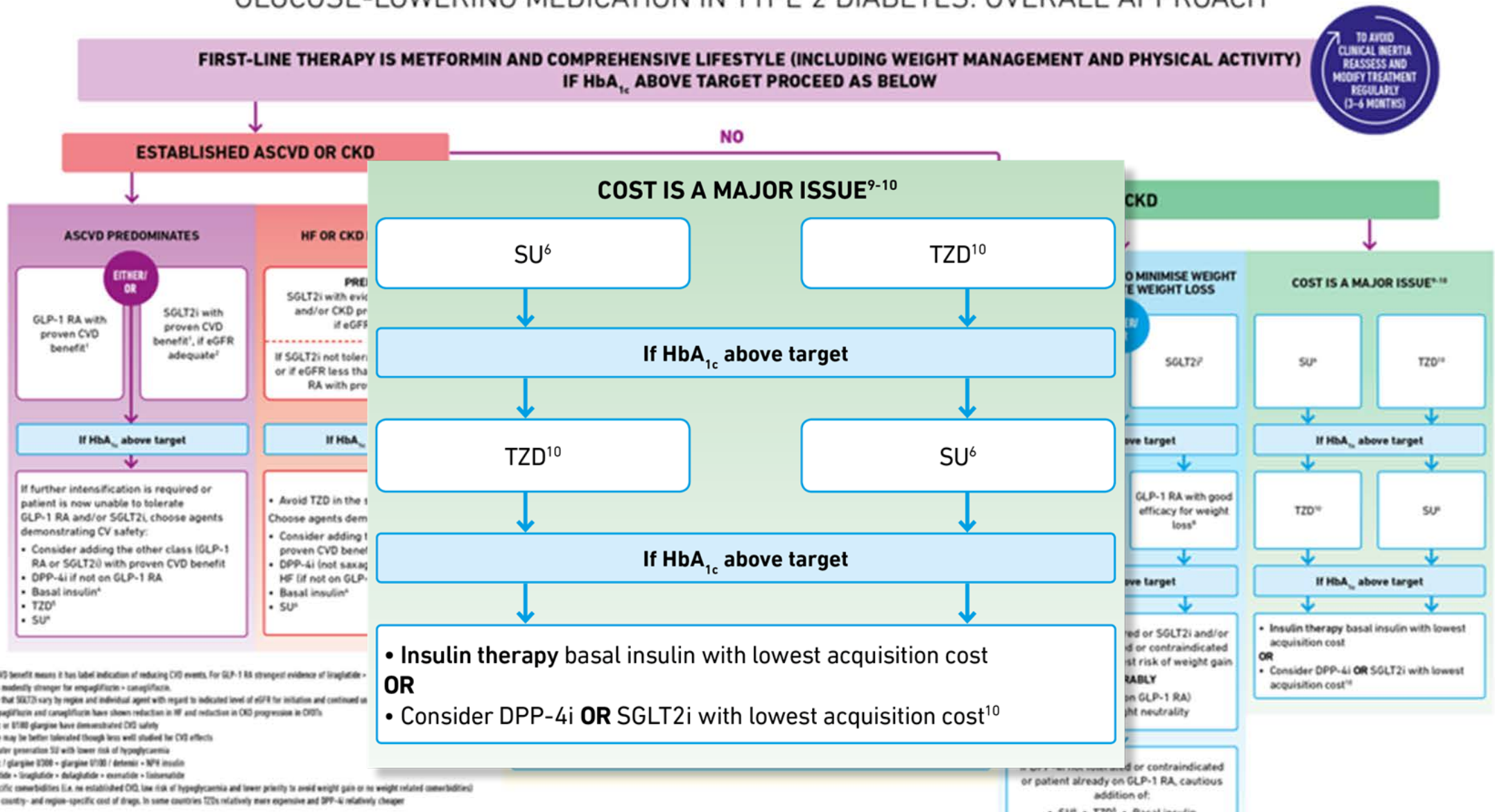
GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



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PRACTICE LEVEL CHANGE: MULTICOMPONENT ORGANIZATIONAL INTERVENTION IN THE PRIMARY CARE SETTING TO IMPROVES OUTCOMES

1. Physician champion
2. Team-based care (that might include site coordinator-facilitated previsit planning)
3. Electronic diabetes registry
4. Visit reminders & patient education
5. Patient-specific physician alerts – decision support
6. Monthly performance review.
7. Outcomes
   - A1C
   - BP
   - Lipid control

Adapted from Diabetes Care. 2008 Dec;31(12):2238-43.

REDUCING THE BURDEN OF T2D

- Helping us raise awareness and understanding of the link between diabetes and cardiovascular disease.

- Positively empowering people to better manage their risk for cardiovascular disease.

- Stay informed with the latest resources and guidelines.
  - AHA/ADA Joint Science Statement
  - ADA Standards of Care
  - ADA Dynamic Journal Articles
  - Quality Improvement

KnowDiabetesByHeart.org

RESOURCES AVAILABLE ON KNOWDIABETESBYHEART.ORG

PATIENT RESOURCES

- Fact sheets & brochures
- Discussion guides
- Living with Type 2 Program
- Ask the Experts Q & A Series

PROFESSIONAL RESOURCES

- Webinars and other non-CME education for health care providers
- Podcast series
- Case studies
- Tools and resources to support adherence to guidelines
- Latest science

American Heart Association.

American Diabetes Association.
Connected for Life

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