Management of Type 2 Diabetes in People With Renal Impairment

Appendix:
Information on Clinical Trials/Studies

Alice YY Cheng, MD, FRCPC

Lance Sloan, MD, MSE, FACE, FASN, FACP

John Anderson, MD

Information on Clinical Trials/Studies: Chapter 1

Acronym	Name	Design	N	Outcomes	Website
NHANES	National Health and Nutrition Examination Survey	A continuous program of studies (combining interviews and physical examinations) to assess the health and nutritional status of adults and children in the US. Combines interviews and physical examinations	~5,000/ year	Various	https://www.cdc.gov/nchs/nhanes/index.htm
VHA	Veterans Health Administration	Largest integrated health care system in the United States	9 million/ year	Various	https://www.va.gov/health/

Information on Clinical Trials/Studies: Chapter 3 (1)

Acronym/Name	Design	N	Primary Outcome	Reference
AASK African American Study of Kidney Disease and Hypertension	African Americans (18–70 years) with hypertensive renal disease randomized to mean arterial pressure goals of either 102–107 or ≤92 mm Hg, and to initial treatment with either a β-blocker (metoprolol), an ACEi (ramipril), or a calcium channel blocker (amlodipine)	1094	Rate of change in GFR; clinical composite of ≥50% reduction from baseline in GFR (or ≥25 mL/min/1.73 m^2), ESRD, or death	Wright JT, Jr., et al. for the AASK Study Group. *JAMA*. 2002; 288:2421–31
ACCORD Action to Control Cardiovascular Risk in Diabetes	Participants with T2D receiving open-label simvastatin randomized to masked fenofibrate or placebo	5518	First occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes	The ACCORD Study Group. *N Engl J Med*. 2010;362:1563–74
ADVANCE Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation	Participants with T2D randomized to standard glucose control or intensive glucose control (to achieve A1C ≤6.5%)	11,140	Composites of major macrovascular events (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) and major microvascular events (new or worsening nephropathy or retinopathy)	The ADVANCE Collaborative Group. *N Engl J Med.* 2008;358:2560–72

A1C, glycated hemoglobin; ACEi, angiotensin-converting enzyme inhibitor; ESRD, end-stage renal disease; GFR, glomerular filtration rate; T2D, type 2 diabetes.

Information on Clinical Trials/Studies: Chapter 3 (2)

Acronym/Name	Design	N	Primary Outcome	Reference
ADVANCE-ON Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation	Survivors of the ADVANCE study were invited to participate in post-trial follow-up	8,494	ESRD (dialysis or kidney transplantation, or death due to kidney disease [overall and by baseline CKD stage]), hypoglycemic episodes, major cardiovascular events, death from other causes	Wong MG, et al. for the ADVANCE-ON Collaborative Group. *Diabetes Care.* 2016;39:694–700
CANVAS Canagliflozin Cardiovascular Assessment Study	The CANVAS Program integrated data from two trials of participants with T2D and high cardiovascular risk who were randomized to canagliflozin or placebo	10,142	Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	Neal B, et al. for the CANVAS Program Collaborative Group. *N Engl J Med.* 2017; 377:644–57
CREDENCE Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation	People with T2D and albuminuric CKD randomized to canagliflozin (100 mg daily) or placebo	4401	Composite of ESRD (dialysis, transplantation, or sustained eGFR of <15 mL/min/1.73 m^2), doubling of serum creatinine level, or death from renal or cardiovascular causes	Perkovic V, et al. for the CREDENCE Trial Investigators. *N Engl J Med.* 2019; 380:2295–306

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; T2D, type 2 diabetes.

Information on Clinical Trials/Studies: Chapter 3 (3)

Acronym/Name	Design	N	Primary Outcome	Reference
DAPA-CKD Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease	Participants with eGFR of 25–75 mL/min/1.73 m^2 and a UACR of 200–5000 randomized to dapagliflozin (10 mg once daily) or placebo	4304	Composite of a sustained decline in the eGFR of ≥50%, ESRD, or death from renal or cardiovascular causes	Heerspink HJL, et al. for the DAPA-CKD Trial Committees and Investigators *N Engl J Med.* 2020; 383:1436–46
DCCT Diabetes Control and Complications Trial	Participants with T1D randomized to intensive therapy (with an external insulin pump or by ≥3 daily insulin injections and guided by frequent blood glucose monitoring) or to conventional therapy (1 or 2 daily insulin injections)	1,441	Appearance and progression of retinopathy and other complications	The Diabetes Control and Complications ~~(DCCT)~~ Trial Research Group. *N Engl J Med*. 1993;329:977–86
DECLARE-TIMI 58 Dapagliflozin Effect on Cardiovascular Events–Thrombolysis In Myocardial Infarction 58	Participants with T2D who had or were at risk for atherosclerotic cardiovascular disease were randomized to dapagliflozin or placebo	17,160	MACE and a composite of cardiovascular death or hospitalization for heart failure	Wiviott SD, et al. for the DECLARE–TIMI 58 Investigators. *N Engl J Med* 2019; 380:347–57

eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; MACE, major adverse cardiovascular event; T1D, type 1 diabetes; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio.

Information on Clinical Trials/Studies: Chapter 3 (4)

Acronym/Name	Design	N	Primary Outcome	Reference
EDIC Epidemiology of Diabetes Interventions and Complications	Multicenter, longitudinal, observational study of DCCT cohort to determine the long-term effects of prior separation of glycemic levels	>1,400	Albumin excretion rate Microalbuminuria ≥30 mg/24 h on 2 consecutive study visits; macroalbuminuria ≥300 mg/day	The DCCT/EDIC Research Group. *Lancet Diabetes Endocrinol*. 2014;2:793–800
EMPA-REG OUTCOME Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose	Participants with T2D at high risk for cardiovascular events randomized to empagliflozin (10 mg or 25 mg) or placebo once daily	7020	Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	Zinman B, et al. for the EMPA-REG OUTCOME Investigators. *N Engl J Med.* 2015; 373:2117–28
IDNT Irbesartan Diabetic Nephropathy Trial	Hypertensive patients with nephropathy due to T2D randomized to irbesartan (300 mg daily), amlodipine (10 mg daily), or placebo. Target BP ≤135/85 mm Hg in all groups	1715	Time to composite of doubling of baseline serum creatinine concentration, development of ESRD, or death from any cause	Lewis EJ, et al. for the Collaborative Study Group. *N Engl J Med*. 2001;345:851–60

BP, blood pressure; DCCT, Diabetes Control and Complications Trial; ESRD, end-stage renal disease; T2D, type 2 diabetes.

Information on Clinical Trials/Studies: Chapter 3 (5)

Acronym/Name	Design	N	Primary Outcome	Reference
RENAAL Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan	Individuals with established nephropathy associated with T2D randomized to losartan (50–100 mg once daily) or placebo, with antihypertensive agents added to achieve a trough BP <140/90 mmHg immediately prior to next dosing	1513	Time to composite end point of doubling of serum creatinine, ESRD, or death	Brenner BM, et al. for RENAAL Study Investigators. *N Engl J Med*. 2001;345:861–9
VADT Veterans Affairs Diabetes Trial	Military veterans with suboptimal response to therapy for T2D randomized to intensive (aim: reduction in A1C of 1.5%) or standard glucose control	1791	Time to first occurrence of MACE, a composite of myocardial infarction, stroke, death from cardiovascular causes, congestive heart failure, surgery for vascular disease, inoperable coronary disease, and amputation for ischemic gangrene	Duckworth W, et al. for the VADT Investigators. *N Engl J Med.* 2009; 360:129–39
UKPDS UK Prospective Diabetes Study	Participants with newly diagnosed T2D randomized to intensive treatment (aim: FPG <6 mmol/L) with a sulphonylurea or insulin, or conventional policy with diet	3867	Any diabetes-related endpoint; diabetes-related death; all-cause mortality	UK Prospective Diabetes Study (UKPDS) Group. *Lancet.* 1998;352:837 –53

A1C, glycated hemoglobin; BP, blood pressure; ESRD, end-stage renal disease; FPG, fasting plasma glucose; MACE, major adverse cardiovascular event; T2D, type 2 diabetes.

Information on Clinical Trials/Studies: Chapter 4 (1)

Acronym/Name	Design	N	Primary Outcome	Reference
ACHIEVE Control	12-month, pragmatic trial in insulin-naïve individuals with T2D and A1C 64–97 mmol/mol (8–11%) after ≥1 year of treatment randomized to insulin glargine 300 U/mL or SOC-BI (insulin glargine 100 U/mL or insulin detemir)	3304	Composite primary endpoint: proportion of participants who attained individualized A1C targets per 2015 HEDIS criteria at 6 months without experiencing hypoglycemia at any time of day during the study	Meneghini LF, et al. *Diabetes Obes Metab*. 2020;22:2004–12
BRIGHT	24-week study in insulin-naive individuals with uncontrolled T2D randomized to evening dosing with insulin glargine 300 U/mL or insulin degludec 100 U/mL), titrated to self-monitored FPG of 80–100 mg/dL	929	A1C change from baseline to week 24	Rosenstock J, et al. *Diabetes Care*. 2018;41:2147–54
CONCLUDE Trial COmparing the efficacy aNd safety of insulin degLUDEc and insulin glargine 300 U/mL in subjects with T2D inadequately treated with basal insulin and oral antidiabetic drugs	Participants with T2D inadequately treated with basal insulin ± oral antidiabetic drugs randomized to insulin degludec 200 U/mL and insulin glargine 300 U/mL	1609	Number of overall symptomatic hypoglycemic events in the maintenance period	Philis-Tsimikas A, et al. on behalf of the CONCLUDE Study Group. *Diabetologia*. 2020:63:698–710

A1C, glycated hemoglobin; FPG, fasting plasma glucose; HEDIS, Healthcare Effectiveness Data and Information Set; SOC-BI, standard-of-care basal insulin;T2D, type 2 diabetes.

Information on Clinical Trials/Studies: Chapter 4 (2)

Acronym/Name	Design	N	Primary Outcome	Reference
DEVOTE Trial Comparing Cardiovascular Safety of Insulin Degludec vs Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events	Participants with T2D at high cardiovascular risk who were randomized to once daily treatment with either insulin degludec or insulin glargine 100 U/mL	7637	Composite: time to first occurrence of an adjudicated major cardiovascular event (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) with a prespecified noninferiority margin of 1.3	Marso SP, et al. for the DEVOTE Study Group. *N Engl J Med*. 2017;377:723–32
EDITION 1-2-3	Adults with T2D were randomized to insulin glargine 300 U/mL or 100 U/mL once daily EDITION 1: basal insulin (≥42 U/d) and prandial insulin therapy ± metformin for ≥1 year EDITION 2: basal insulin (≥42 U/d) in combination with oral antidiabetic agents EDITION 3: oral antidiabetic agents for ≥6 months before screening and insulin-naïve	 807 811 878	Change from baseline in A1C	 Riddle MC, et al. *Diabetes Care*. 2014;37:2755–62 Yki-Järvinen H, et al. *Diabetes Care*. 2014;37:3235–43 Bolli GB, et al. *Diabetes Obes Metab*. 2015;17:386–94

A1C, glycated hemoglobin; T2D, type 2 diabetes.