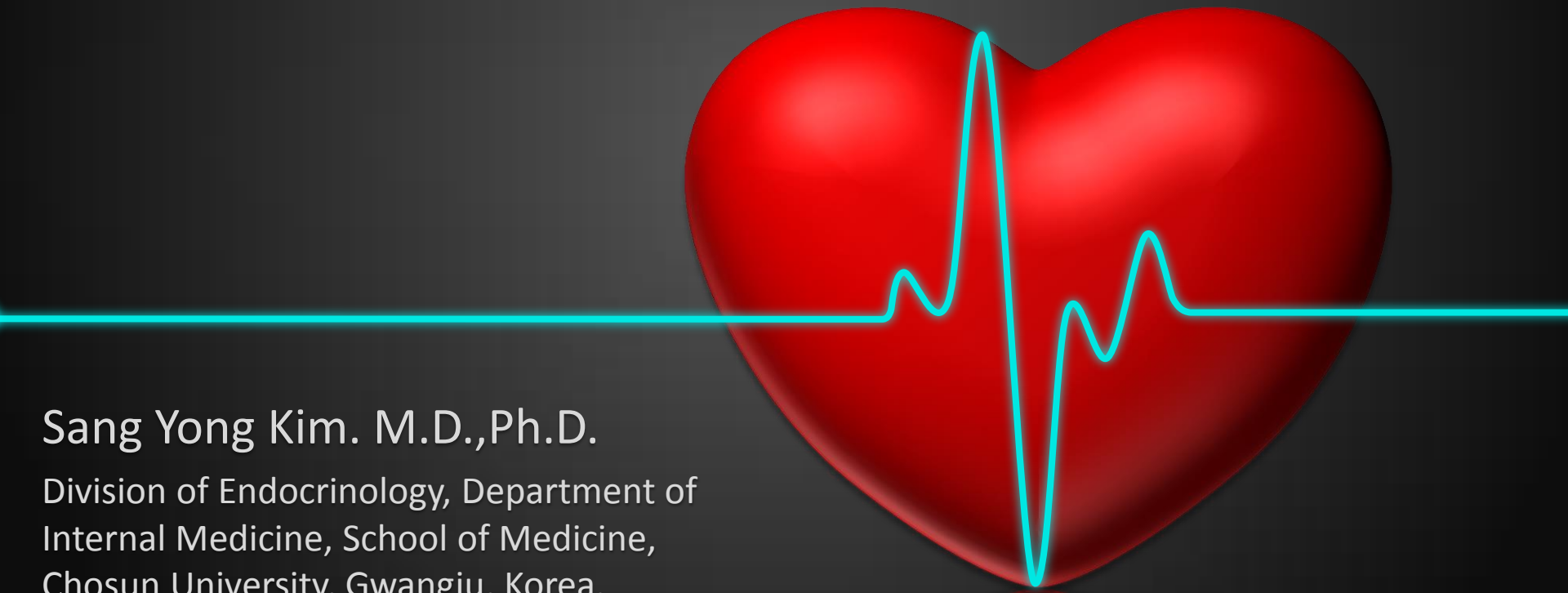
Glucose control for prevention of Cardiovascular disease : lesson from large clinical trials



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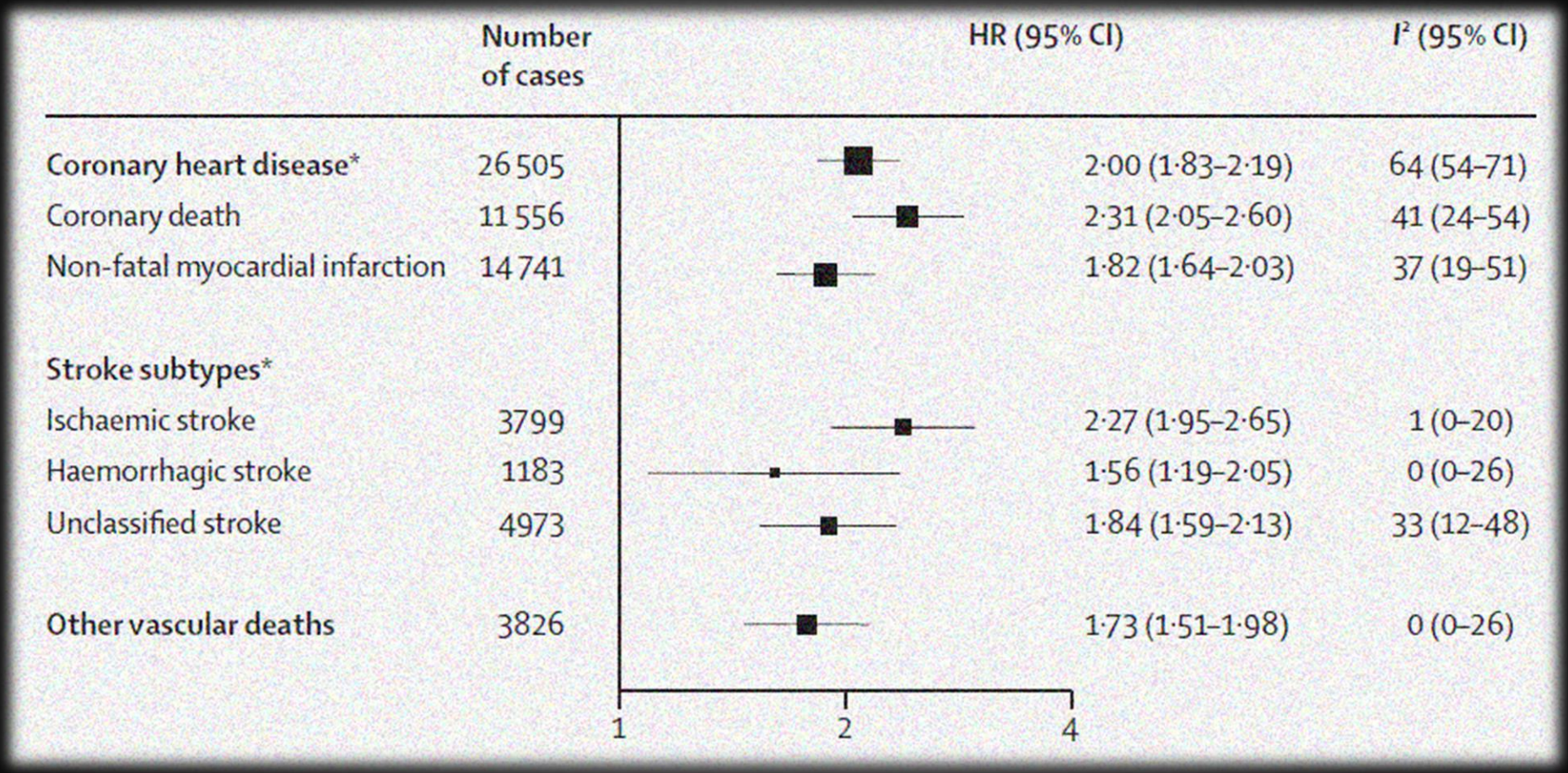
Conflict of interest disclosure

None

Committee of Scientific Affairs

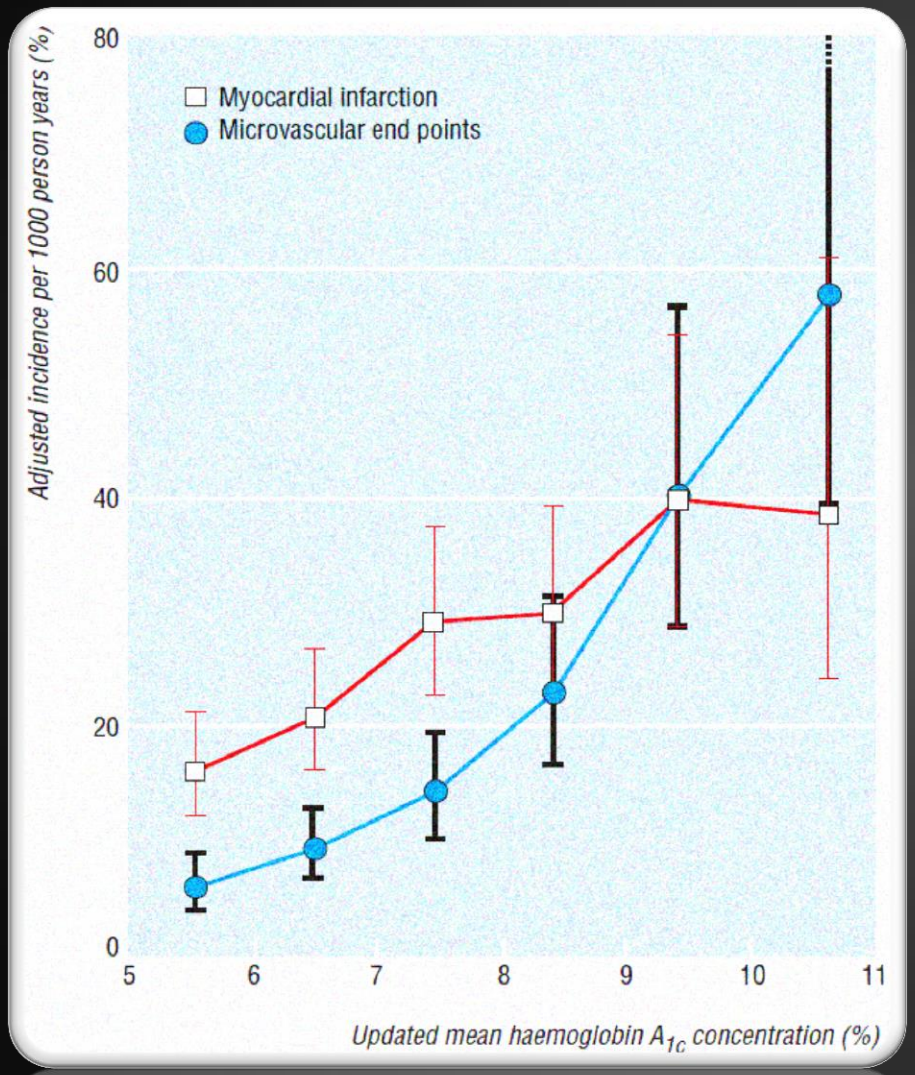
Diabetes and Cardiovascular disease

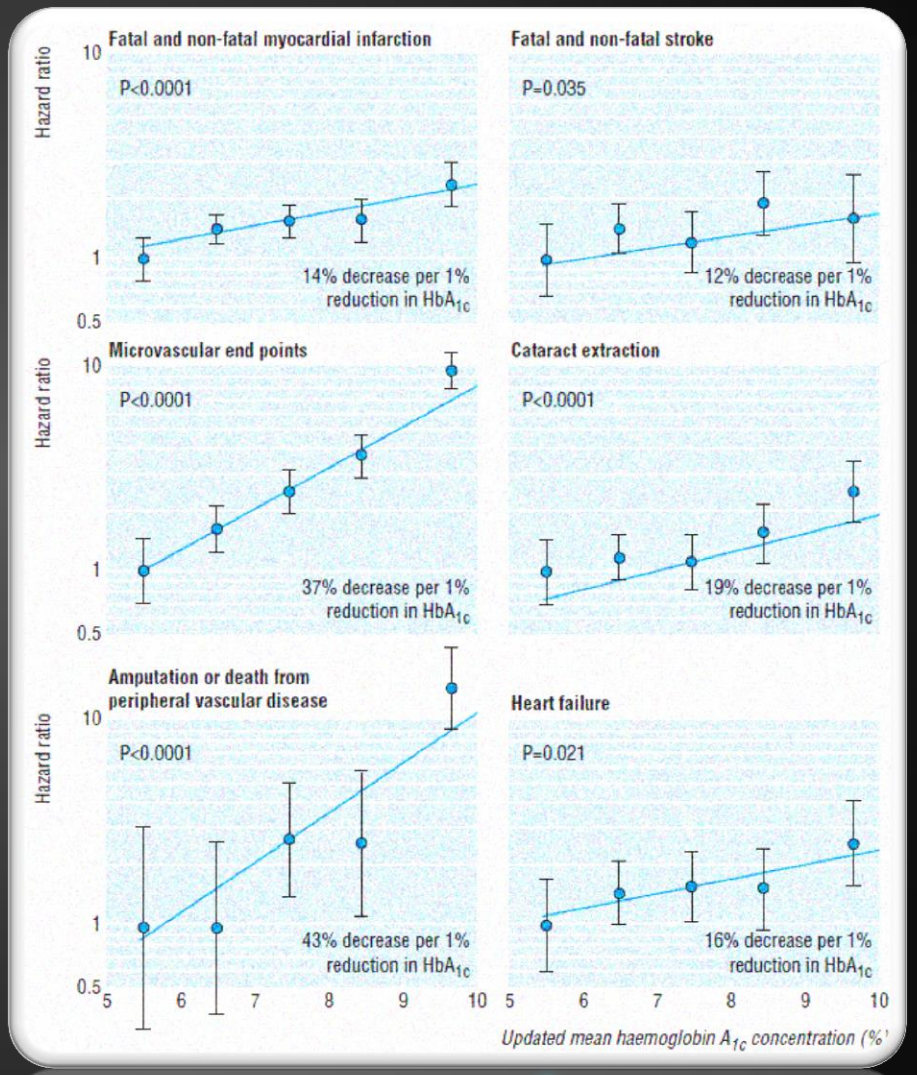


Hazard ratios(HRs) for vascular outcomes in people with versus those without diabetes at baseline

lancet 2010;375:2215-2222

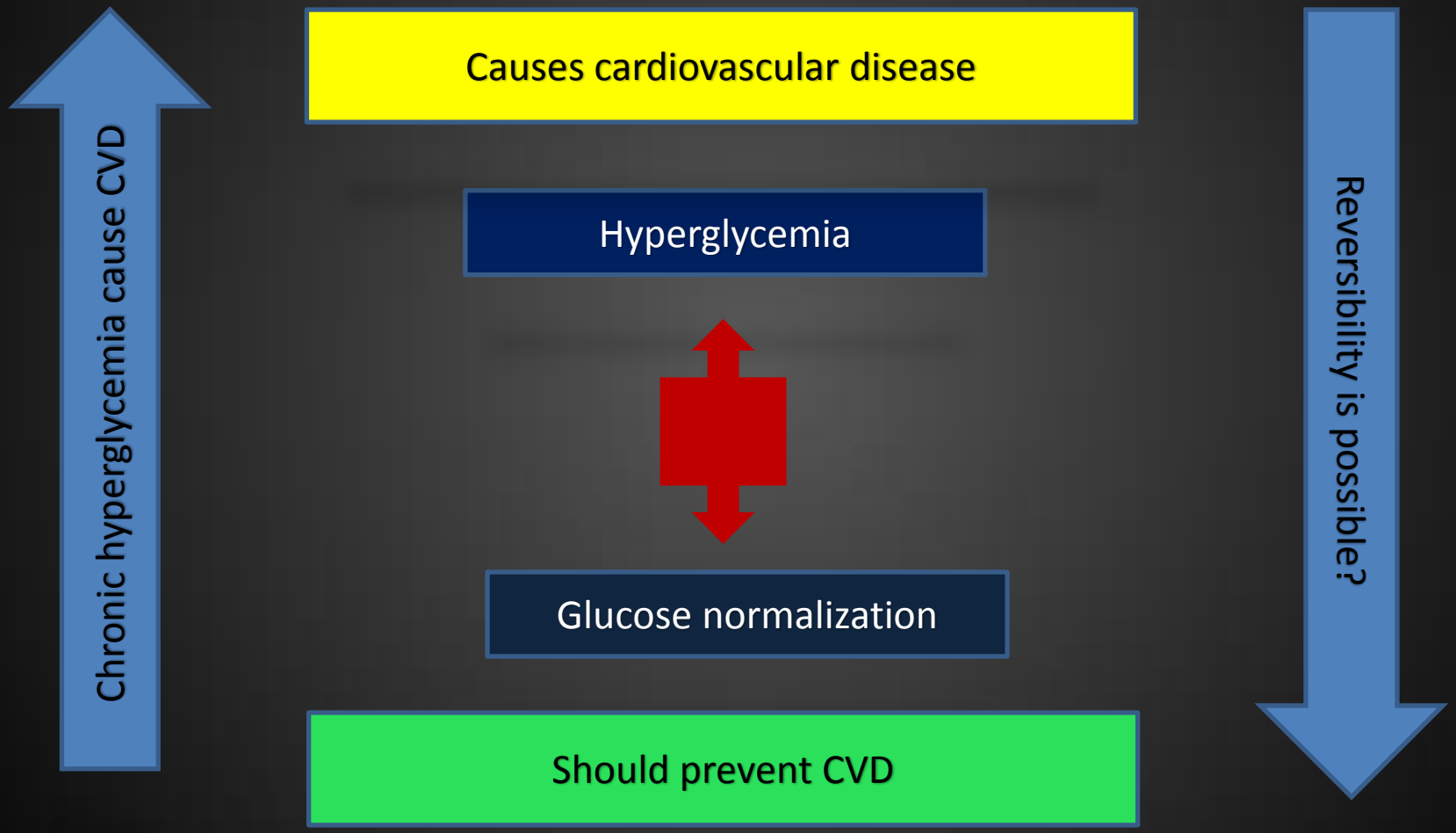
UKPDS: HbA1c and rates for MI and microvascular complications





BMJ. 2000;321(7258):405-12

Hyperglycemia and CVD risk



Glucose lowering and vascular benefits

Older trials

Demonstrating a positive impact of tight glycemic control on macrovascular disease in later follow-up period.

- DCCT/EDIC
- UKPDS

More recent trials

Demonstrating neutral/negative effects of tight glycemic control in patients with T2DM

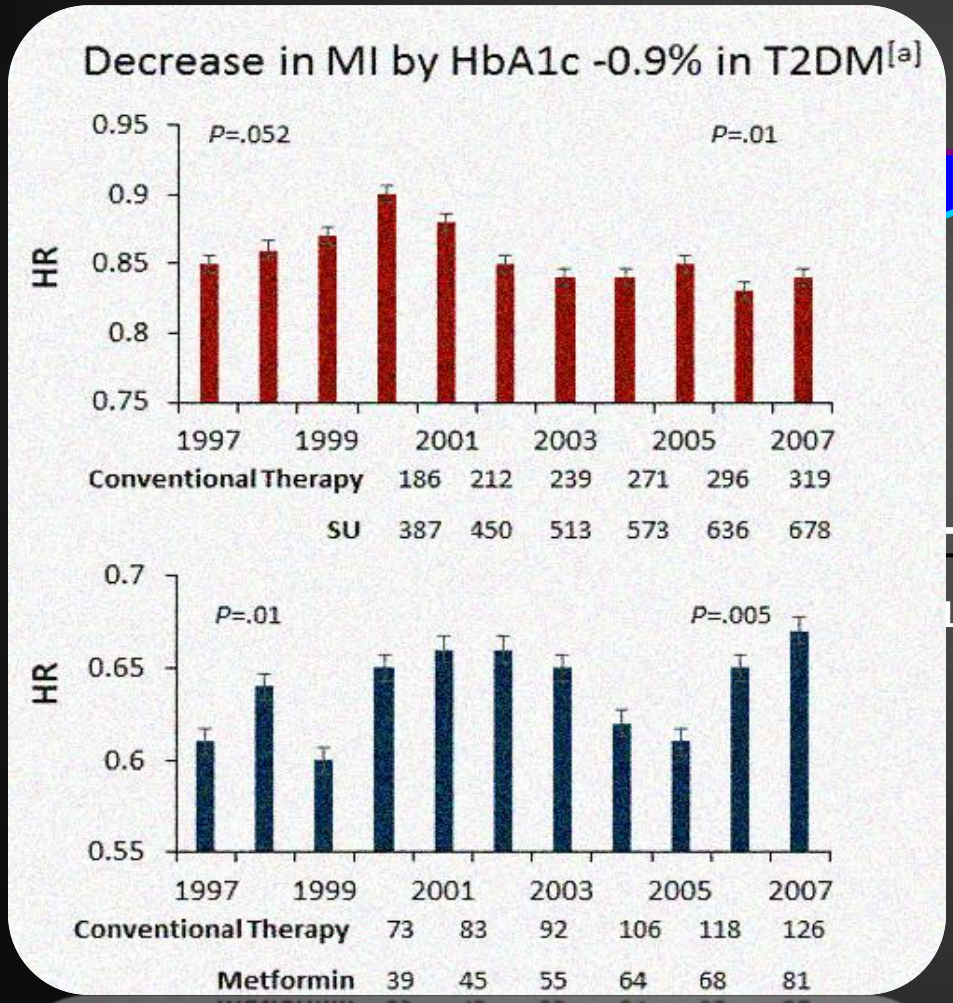
- ACCORD
- ADVANCE
- VADT

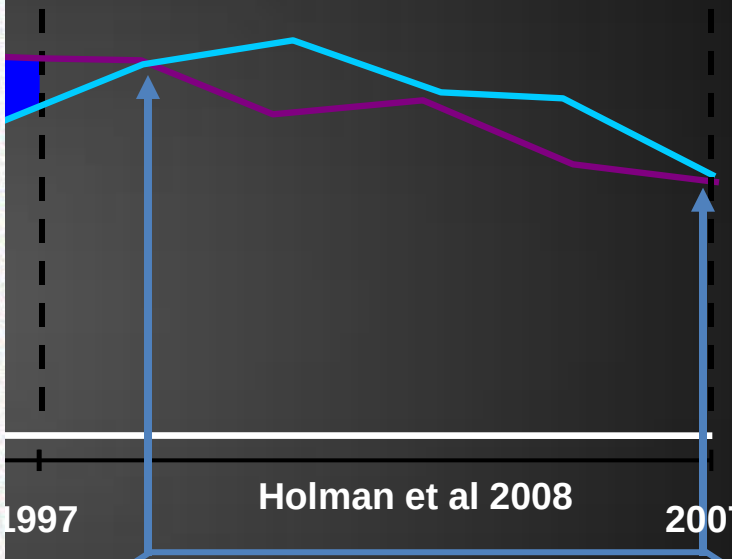
Comparison of major trials of intensive glucose control and CV outcomes

	UKPDS33	UKPDS34	ACCORD	ADVANCE	VADT
Subject No.	3,867	753	10,252	11,140	1791
Age(y)	53	53	62	66	60
Duration of diabetes(y)	0	0	10	8	11.5
History of CV disease(%)	NR	NR	35	32	40
HbA1c at baseline(%)	7.08	7.0	8.1	7.2	9.4
Duration of F/U(y)	10	10.7	3.7	5	5.6
Achieved HbA1c(%)	7.0 vs 7.9	7.4 vs 8.0	6.4 vs 7.5	6.3 vs 7.0	6.9 vs 8.5
HR for primary outcome	MI : 0.84 (0.71–1.00) NS Stroke :1.11(0.81-1.51) NS	MI : 0.61 (0.41-0.89) p=0.01 Stroke : 0.59(0.29-1.18) NS	0.90 (0.78–1.04) NS	0.94 (0.84–1.06) NS	0.88 (0.74–1.05) NS
HR for all-cause mortality	0.94 (0.80–1.10) NS	0.66 (0.45-0.91) p=0.011	1.22 (1.01–1.46) p = 0.02	0.93 (0.83–1.06) NS	1.07 (0.81–1.42) NS

Modified table from Diabetes care 2012:34;202-34

Achieving early glycaemic control may generate a "good legacy effect" in UKPDS post-trial





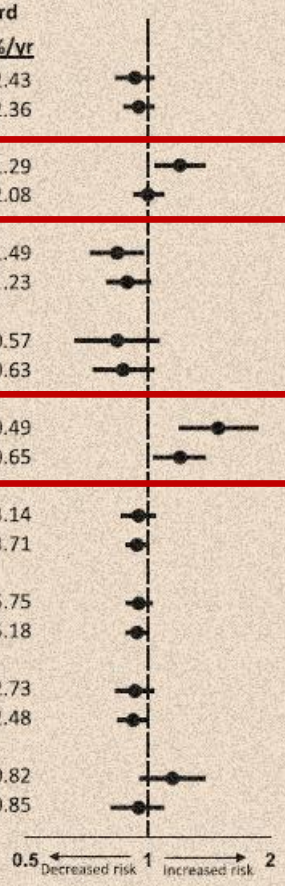
Difference in HbA1c was lost after first year but patients in the initial intensive arm still had lower incidence of any complication:

- **24% reduction in microvascular complications**
- **15% reduction in MI**
- **13% reduction in all-cause mortality**

N Engl J Med. 2008; 359: 1577–1589; UKPDS 33. *Lancet*. 1998; 352: 837–853.

ACCORD post-trial F/U (ACCORDION)

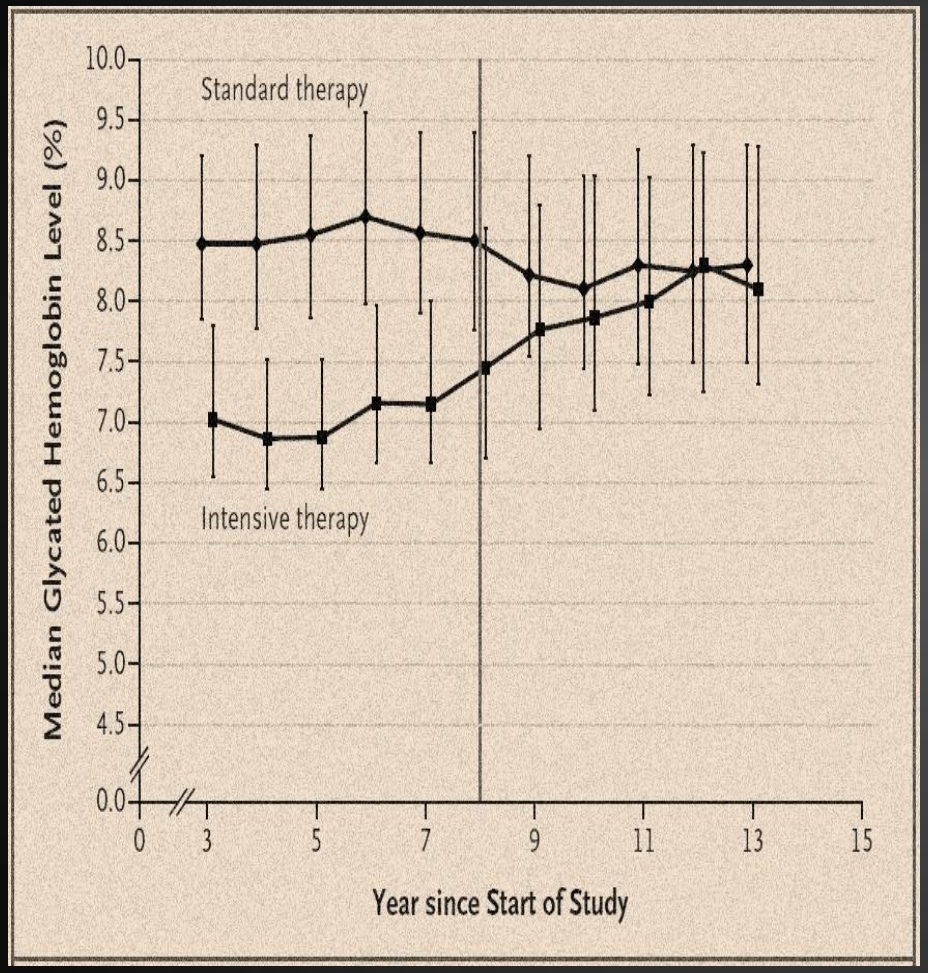
		Intensive		Standard		HR (95%CI)	P
		N	%/yr	N	%/yr		
Primary Outcome	During ACCORD	546	2.26	582	2.43	0.93 (0.83, 1.04)	0.22
	During Full Follow-up	896	2.25	930	2.36	0.95 (0.87, 1.04)	0.27
Death	During ACCORD	391	1.55	327	1.29	1.20 (1.04, 1.39)	0.01
	During Full Follow-up	980	2.09	978	2.08	1.01 (0.92, 1.10)	0.91
Nonfatal MI	During ACCORD	303	1.24	360	1.49	0.84 (0.72, 0.98)	0.02
	During Full Follow-up	444	1.10	492	1.23	0.89 (0.79, 1.02)	0.09
Nonfatal Stroke	During ACCORD	119	0.48	142	0.57	0.84 (0.66, 1.07)	0.16
	During Full Follow-up	227	0.55	261	0.63	0.87 (0.73, 1.04)	0.11
Cardiovascular Death	During ACCORD	185	0.73	125	0.49	1.49 (1.19, 1.87)	<0.01
	During Full Follow-up	364	0.78	305	0.65	1.20 (1.03, 1.40)	0.02
Primary or Any Death	During ACCORD	722	2.99	753	3.14	0.95 (0.86, 1.05)	0.34
	During Full Follow-up	1407	3.50	1472	3.71	0.94 (0.88, 1.02)	0.12
Primary or Revascularization or Congestive Heart Failure	During ACCORD	1210	5.47	1269	5.75	0.95 (0.88, 1.03)	0.21
	During Full Follow-up	1700	4.84	1792	5.18	0.94 (0.88, 1.00)	0.05
Cardiovascular Death or MI or Unstable Angina	During ACCORD	606	2.54	647	2.73	0.93 (0.83, 1.04)	0.21
	During Full Follow-up	898	2.27	961	2.48	0.92 (0.84, 1.01)	0.08
Congestive Heart Failure Hospitalization	During ACCORD	233	0.83	203	0.82	1.15 (0.95, 1.39)	0.14
	During Full Follow-up	340	0.81	356	0.85	0.95 (0.81, 1.10)	0.45

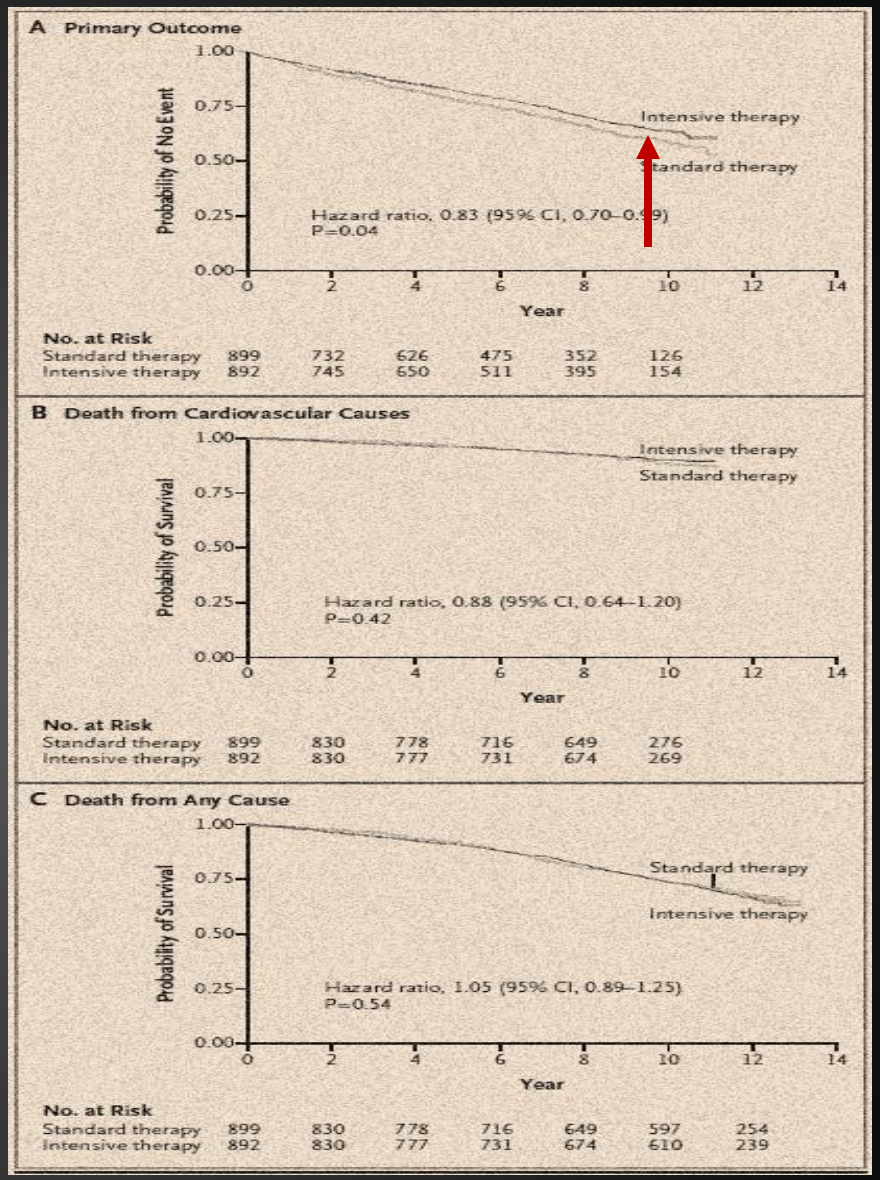


More than 8,000 peoples were monitored for a median of 8.8 years from randomization. At the end of the ACCORDION follow-up, the gap of HbA1c levels were decreased to 7.8% in intensive and 8.0% in conventional group.

Diabetes Care 2016;39:701–708

VADT post-trial F/U

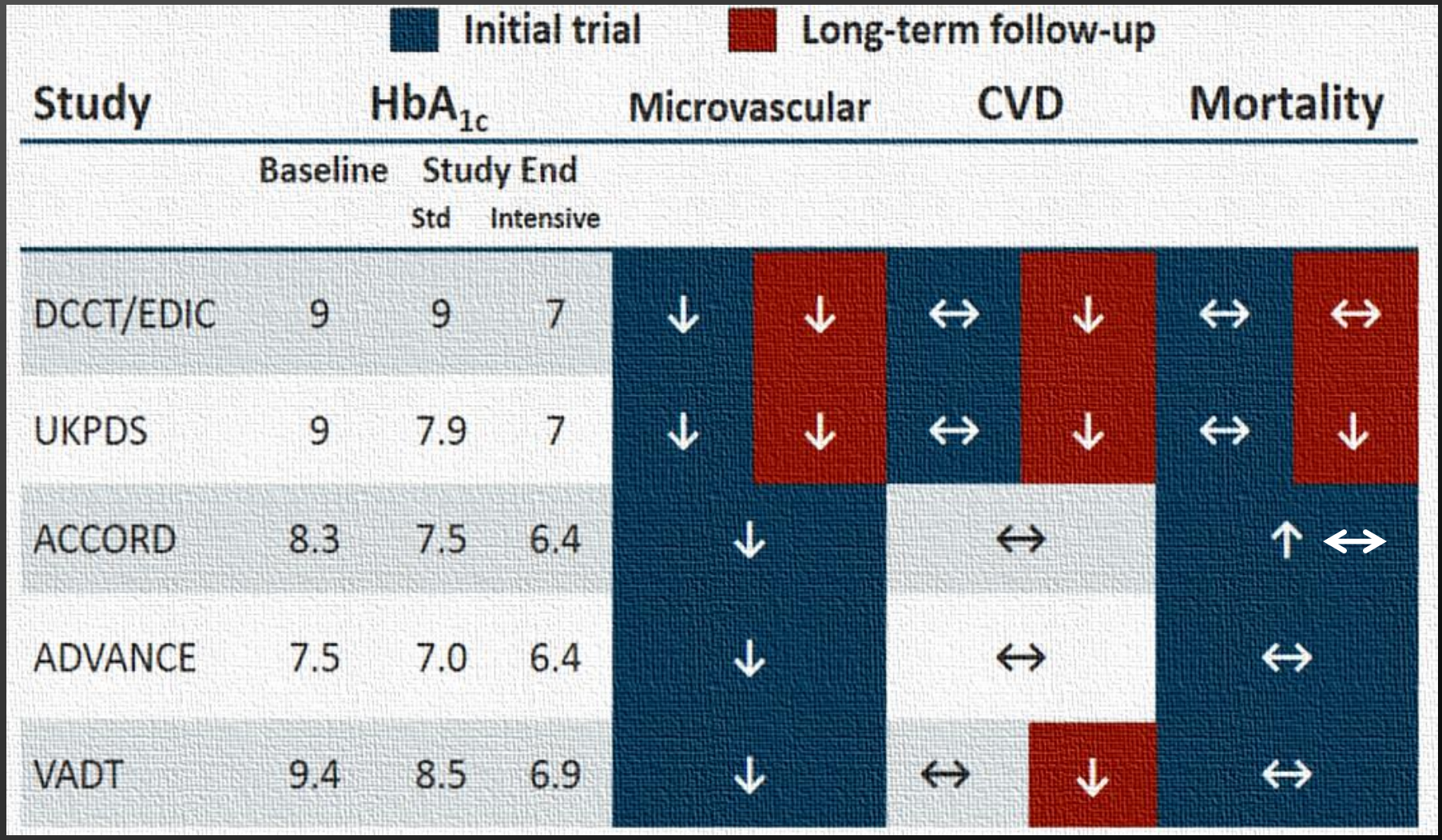




Over a median follow-up of 10 years, the intensive-therapy reduce the primary outcome by 17% significantly, but did not have reduced cardiovascular mortality and all-cause mortality.

N Engl J Med 2015;372:2197-206.

Impact of intensive therapy in diabetes in major clinical trials



Am J Med. 2010;123:374e9-e18

Meta-analyses of the main trials

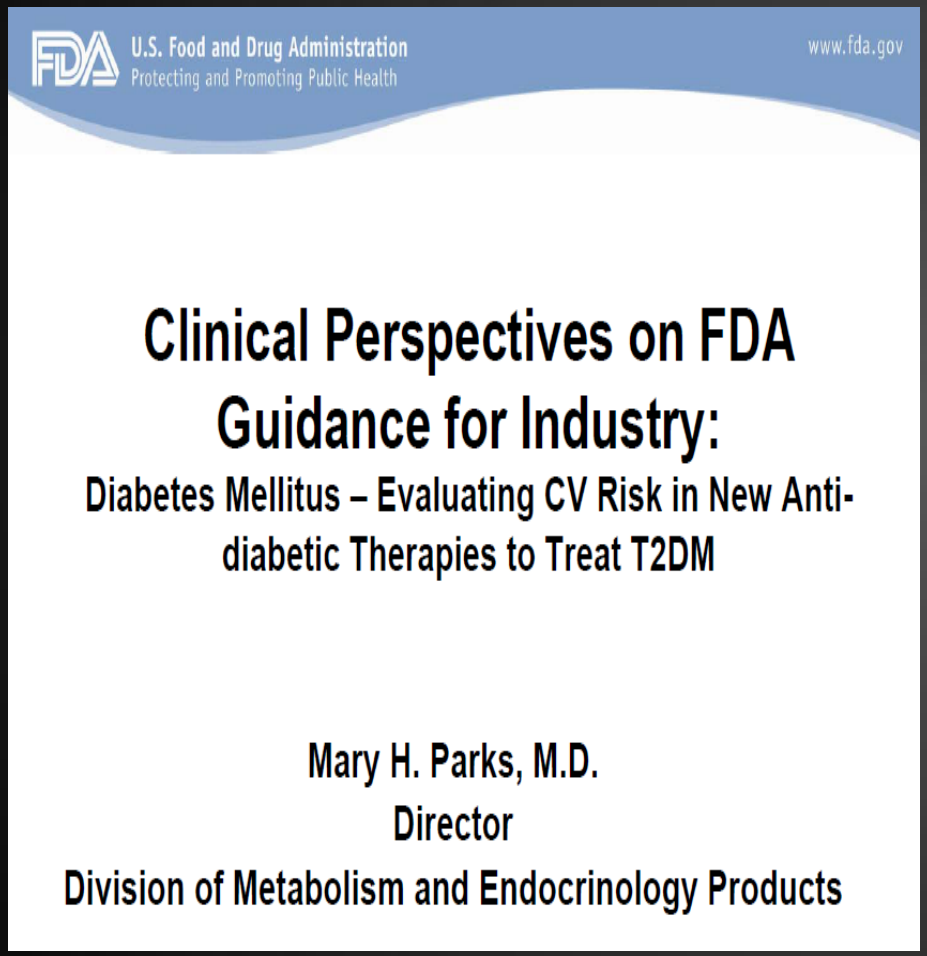
Meta-analysis	Trial	No.	Absolute decreased in HbA1c	Effects of intensive glycemic control		
				MI	Mortality	Hypoglycemia
Ray et al.	UKPDS(33+34 combined) PROactive ACCORD ADVANCE VADT	33,040	0.9%	OR 0.85 (0.77–0.93)	OR 1.02 (0.87–1.19)	NR
Kelly et al.	UKPDS33 UKPDS34 ACCORD ADVANCE VADT	27,802	0.8%	OR 0.89 (0.81–0.96)	OR 0.98 (0.84–1.15)	OR 2.3 (1.46–2.81)
Mannucci et al.	UKPDS(33+34 combined) PROactive ACCORD ADVANCE VADT	32,632	0.9%	OR 0.86 (0.78–0.93)	OR 0.98 (0.77–1.23)	OR 3.01 (1.47–4.60)
Turnbull et al.	UKPDS 33 ACCORD ADVANCE VADT	27,049	0.9%	HR 0.85 (0.76–0.94)	HR 1.04 (0.90–1.20)	HR 2.48 (1.91–3.21)

Diabetes care 2012:34;202-34

Persistent questions in diabetes related to CV events

- Although there are some data suggestive of a possible CV protective effect of intensive glycemic control after long-term follow-up, these data are not consistent.
- Different strategies and characteristics of population of each trials make it difficult to elicit a definite conclusion.
- And also, increased mortality of ACCORD trial could not explain appropriately despite several reasons have been suggesting.
- In addition, some anti-diabetic agents were suspected to worsen cardiovascular outcomes(eg, rosiglitazone, muraglitazar).

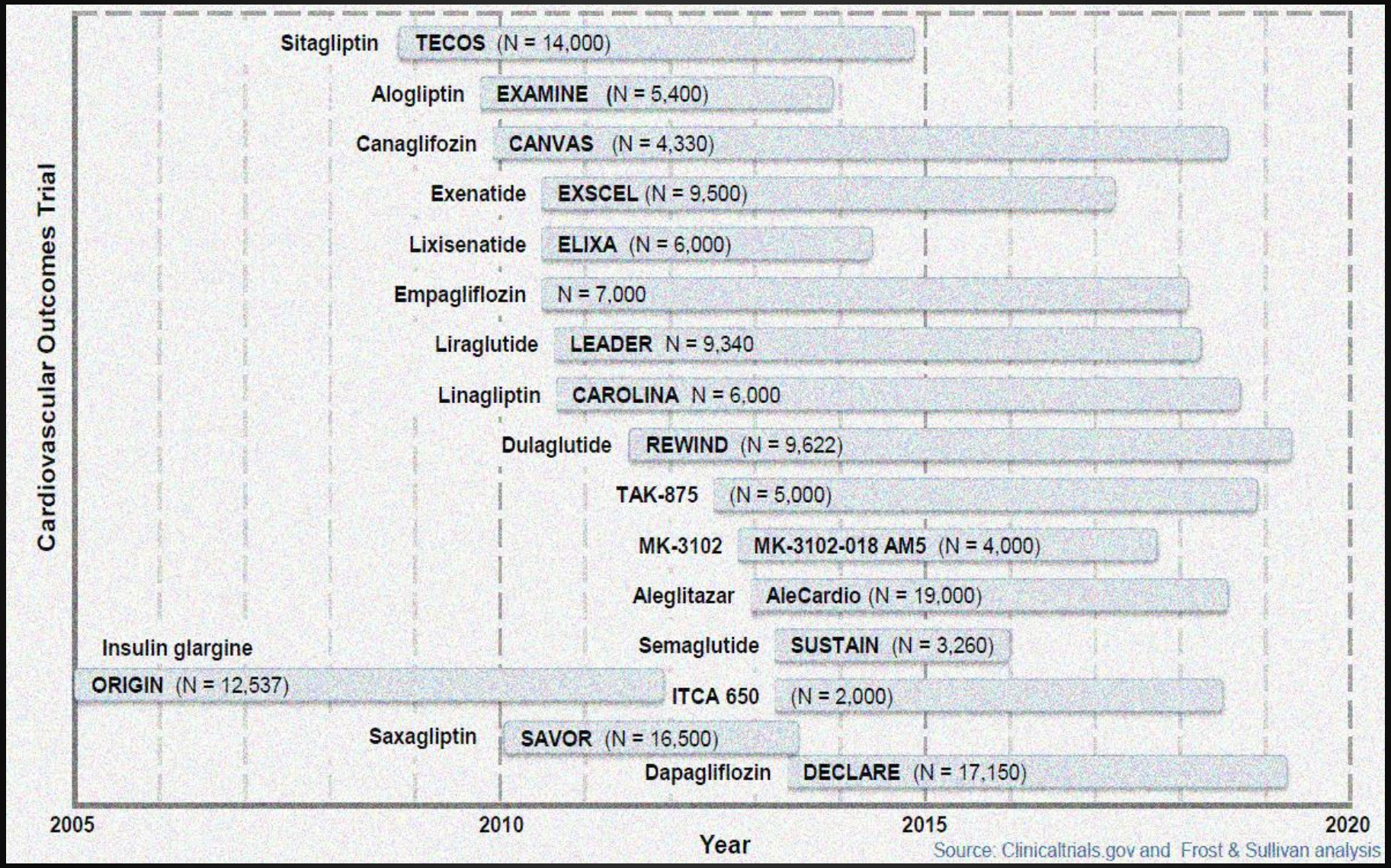
Regulatory obligations for all new diabetes medications: 2008



1. An upper bound of the 95% CI for the risk ratio of important CV events of ,1.3 should be used as a key criterion for excluding unacceptable CV risk for new treatments of type 2 diabetes.
2. Study patients must include those with relatively advanced disease, elderly patients, and patients with some degree of renal impairment.
3. A minimum of 2 years' CV safety data must be provided.
4. All phase 2 and 3 studies should include a prospective, independent adjudication of CV events. Adjudicated events should include CV mortality, myocardial infarction(MI), and stroke and can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other end points.
5. For satisfaction of the new statistical guidelines, the analysis of CV events may include a meta-analysis of all placebo-controlled trials, add-on trials (i.e., drug vs. placebo, each added to standard therapy), and active-controlled trials or an additional single large safety trial may be conducted that alone, or added to other trials, would be able to satisfy this upper bound before New Drug Application/Biologic License Application submission.

http://www.fda.org/downloads/Drugs/NewsEvents/UCM209087.pdf

Cardiovascular outcomes trials timeline



DPP-4 inhibitors Trials

: SAVOR-TIMI, EXAMINE, and TECOS

Saxaglliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus- Thrombolysis in Myocardial Infaction

Examination of Cardiovascular Outcomes with Alogliptin vs Standard of Care

Trial Evaluating Cardiovascular Outcomes with Sitagliptin

SAVOR, EXAMINE, and TECOS

Key results

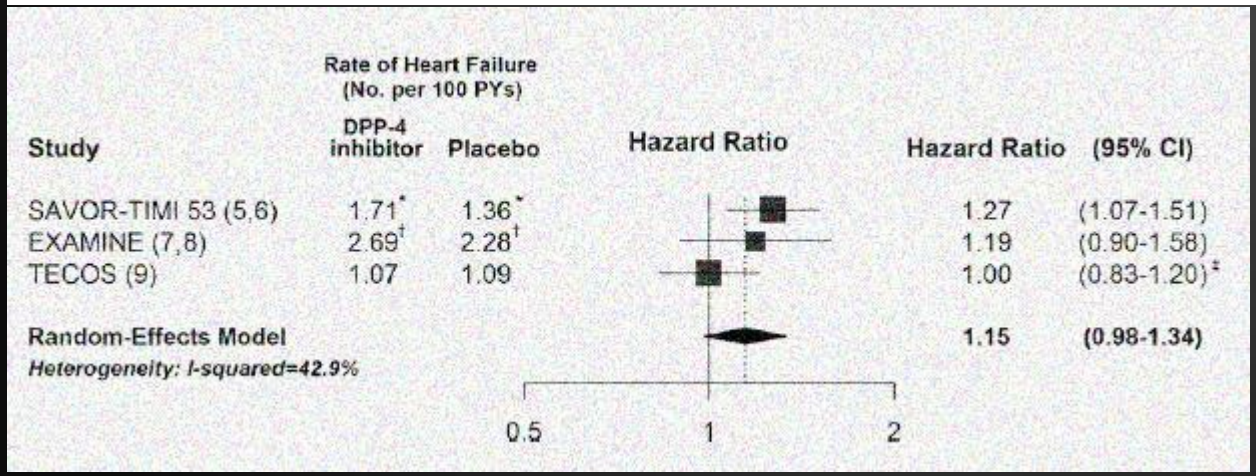
	SAVOR-TIMI	EXAMINE	TECOS
Agents	Saxagliptin vs Placebo	Alogliptin vs placebo	Sitagliptin vs placebo
Median F/U	2.1 years	18months	3.0 years
HbA1c change	Saxa 7.7 ± 1.4% Placeb0 7.9 ± 1.5%	LS mean difference -0.36%(95% CI: -0.43, -0.28; P < .001)	LS mean difference -0.29%(95% CI: -0.32, -0.27)
CV outcome Primary Secondary	 HR 1.00(0.89, 1.27); NS HR 1.02(0.94, 1.11); NS	 HR 0.96(≤ 1.16);NS HR 0.95(≤ 1.14);NS	 HR 0.98(0.88, 1.09); NS HR 0.99(0.89, 1.11); NS
HF hospitalization	1.27(1.07-1.51)	1.19(0.9-1.58)	1.09(0.83-1.20)
Other S/E	No difference in incidence of acute and chronic pancreatitis; fewer cases of pancreatic cancer in Saxa group.	No difference in incidence of acute and chronic pancreatitis, cancer, renal impairment, angioedema, or sever hypoglycemia	No difference in incidence of infection, cancer, renal failure, hypoglycemia, or nonCV death

DPP-4 inhibitors and HF

Table 1—Data from randomized placebo-controlled trials of DPP-4 inhibitors and the risk of HF

Study	Year	DPP-4 inhibitor	Population	Sample size	Median follow-up (years)	Hospitalization for HF: Rate (no. per 100 PYs) DPP-4 inhibitor	Hospitalization for HF: Rate (no. per 100 PYs) Placebo	Hospitalization for HF: HR (95% CI)
SAVOR-TIMI 53 (5,6)	2013, 2014	Saxagliptin	CVD or multiple CVD risk factors	16,492	2.1	1.71*	1.36*	1.27 (1.07–1.51)
EXAMINE (7,8)	2013, 2015	Alogliptin	Post-ACS	5,380	1.5	2.69†	2.28†	1.19 (0.90–1.58)
			With history of HF	1,533		5.60†	5.85†	1.00 (0.71–1.42)
			With no history of HF	3,847		1.53†	0.86†	1.76 (1.07–2.90)
TECOS (9)	2015	Sitagliptin	CVD	14,671	3.0	1.07	1.09	1.00 (0.83–1.20)‡

ACS, acute coronary syndrome; PYs, person-years. *Estimated using the total person-years of follow-up reported for each group (16,884 for saxagliptin and 16,761 for placebo). †Estimated using the median duration of follow-up for the trial. ‡Adjusted for baseline history of HF.



FDA drug safety communication
April 5, 2016

- FDA adds warnings about HF risk to labels of T2DM medicines containing saxagliptin and alogliptin.

- Health care professionals should consider discontinuing medications containing saxagliptin and alogliptin in patients who develop heart failure and monitor their diabetes control.
- If a patient's blood sugar level is not well-controlled with their current treatment, other diabetes medicines may be required.
- Patients taking these medicines should contact their health care professionals right away if they develop signs and symptoms of heart failure such as:
  - Unusual shortness of breath during daily activities
  - Trouble breathing when lying down
  - Tiredness, weakness, or fatigue
  - Weight gain with swelling in the ankles, feet, legs, or stomach
- Patients should not stop taking their medicine without first talking to their health care professionals.

*www.**fda**.gov/Drugs/DrugSafety/ucm486096.htm*

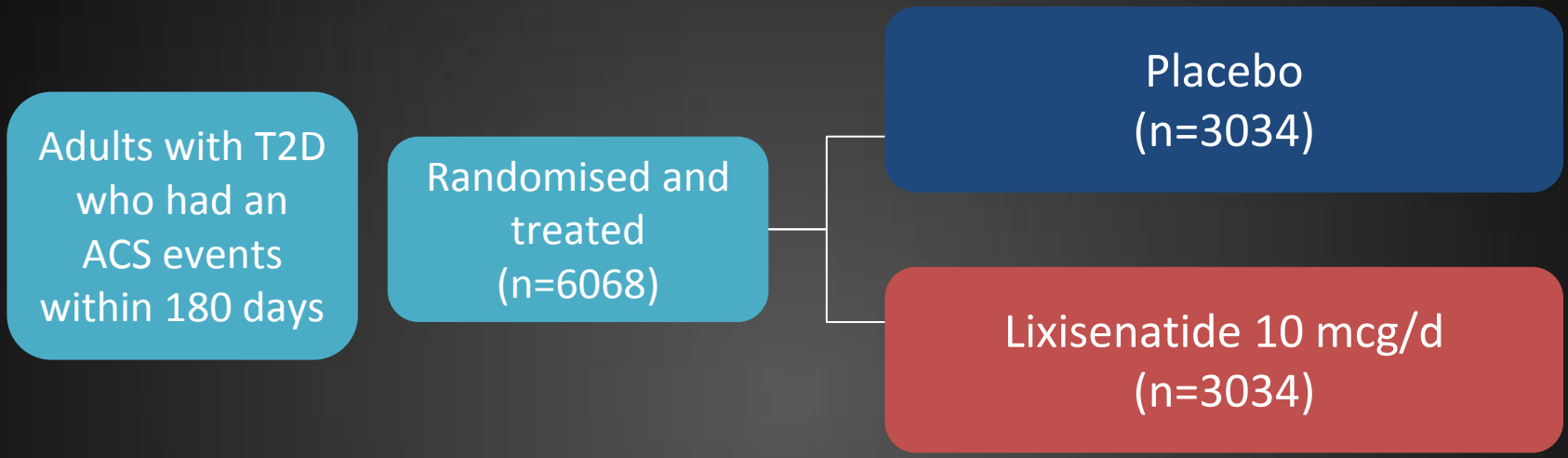
Ongoing DPP-4 inhibitor trials

Study	CAROLINA
DPP-4 i	Linagliptin
Comparator	Sulfonylurea
N	6000
Estimated completion date	Sep, 2018

Study	CARMELINA
DPP-4 i	Linagliptin
Comparator	Placebo
N	8300
Estimated completion date	Jan, 2018

Clinicaltrials.gov.

ELIXA trial
study design



- Phase 3b randomized, double-blind, placebo-controlled, multicenter study
- Run-in = 7 days for training in self-administration drug
- Outcomes;
  Primary composite: MACE + hospitalization for unstable angina
  Secondary & Others
  - Primary + hospitalization for HF
  - Primary + hospitalization for HF + coronary revascularization
  - % change ACR to week 108
  - All-cause of death
- Median follow-up : 25 months

N Engl J Med 2015;373:2247-57

ELIXA trial

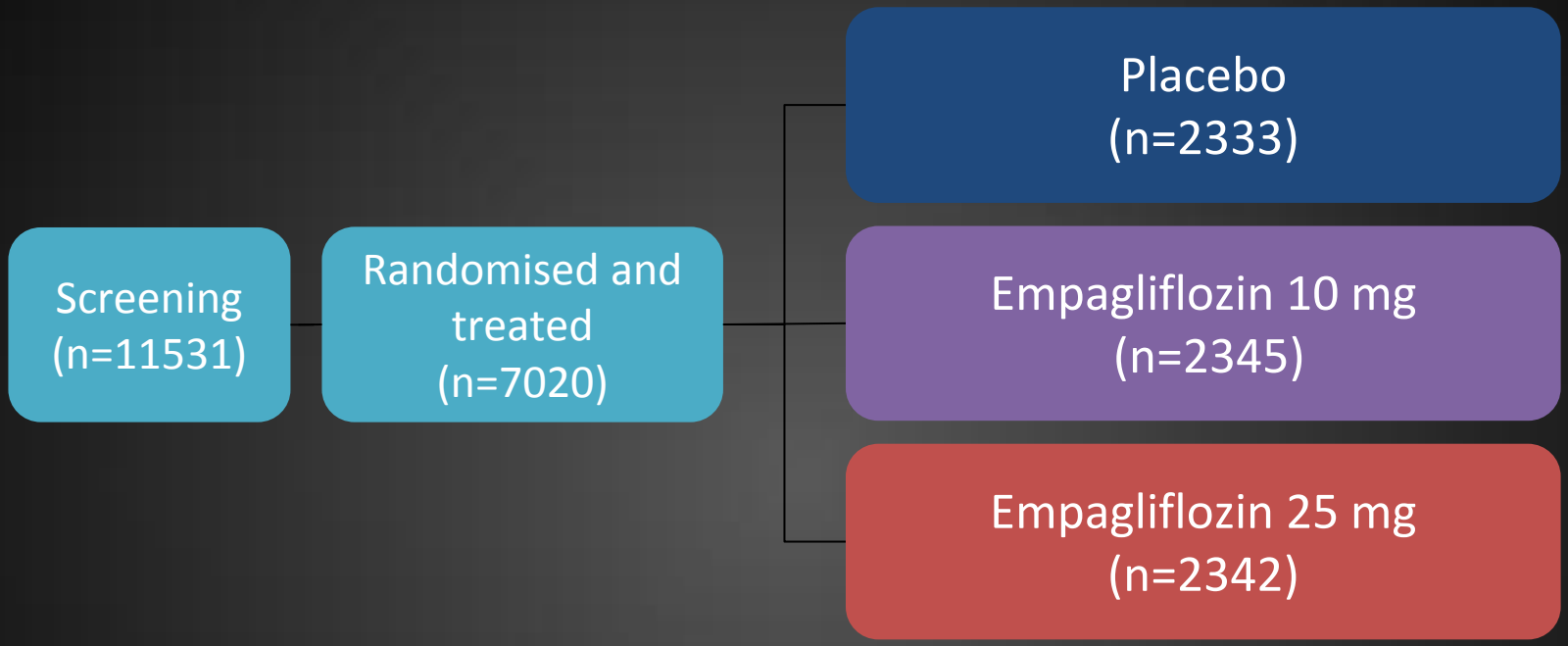
Results

Table 2. Incidence Rates and Hazard Ratios, with Adjustment for Geographic Region, for the Primary Composite End Point, Its Components, and Other Efficacy Outcomes.

End Point	Placebo (N = 3034)		Lixisenatide (N = 3034)		Adjusted Hazard Ratio (95% CI)	P Value
	Patients with Event	No. of Events/ 100 Patient-Yr	Patients with Event	No. of Events/ 100 Patient-Yr		
Primary end point: death from cardiovascular causes, nonfatal stroke, nonfatal myocardial infarction, or unstable angina — no. (%)	399 (13.2)	6.3	406 (13.4)	6.4	1.02 (0.89–1.17)	0.81
Components of primary end point — no./total no. (%)						
Death from cardiovascular causes	93/399 (23.3)	—	88/406 (21.7)	—	—	—
Nonfatal myocardial infarction	247/399 (61.9)	—	255/406 (62.8)	—	—	—
Nonfatal stroke	49/399 (12.3)	—	54/406 (13.3)	—	—	—
Unstable angina	10/399 (2.5)	—	9/406 (2.2)	—	—	—
Patients with each primary end-point event — no. (%)*						
Death from cardiovascular causes	158 (5.2)	2.4	156 (5.1)	2.3	0.98 (0.78–1.22)	0.85
Myocardial infarction	261 (8.6)	4.1	270 (8.9)	4.2	1.03 (0.87–1.22)	0.71
Stroke	60 (2.0)	0.9	67 (2.2)	1.0	1.12 (0.79–1.58)	0.54
Unstable angina	10 (0.3)	0.1	11 (0.4)	0.2	1.11 (0.47–2.62)	0.81
Secondary end points — no. (%)						
Primary end-point event or hospitalization for heart failure	469 (15.5)	7.6	456 (15.0)	7.3	0.97 (0.85–1.10)	0.63
Primary end-point event, hospitalization for heart failure, or revascularization	659 (21.7)	11.2	661 (21.8)	11.1	1.00 (0.90–1.11)	0.96
Additional end points — no. (%)						
Hospitalization for heart failure	127 (4.2)	1.9	122 (4.0)	1.8	0.96 (0.75–1.23)	0.75
Death from any cause	223 (7.4)	3.3	211 (7.0)	3.1	0.94 (0.78–1.13)	0.50

N Engl J Med 2015;373:2247-57

EMPA-REG outcome trial



Primary outcome

3-point MACE: Time to first occurrence of CV death, non-fatal MI or non-fatal stroke

Key secondary outcome

4-point MACE: Time to first occurrence of CV death, non-fatal MI, non-fatal stroke or hospitalization for unstable angina

Further pre-specified outcomes

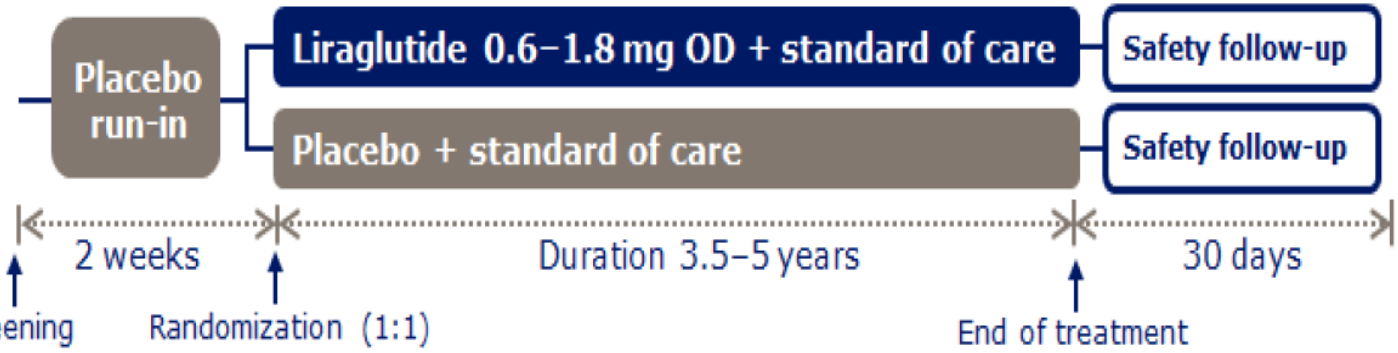
- CV death, Non-fatal MI, Non-fatal stroke, Hospitalization for heart failure, All-cause mortality

N Engl J Med 2015;373:2117-28.

LEADER trial

9340 subjects

- Double blinded
- 2-week placebo run-in



Key inclusion criteria

- T2DM, HbA_{1c} ≥7.0%
- Antidiabetic drug naïve; OADs and/or basal/premix insulin
- Age ≥50 years and established CV disease or chronic renal failure

or

- Age ≥60 years and risk factors for CV disease

Primary objective

To assess the effect of treatment with liraglutide compared with placebo on the incidence of CV events in adults with T2DM that are at high risk for CV events

Primary endpoint

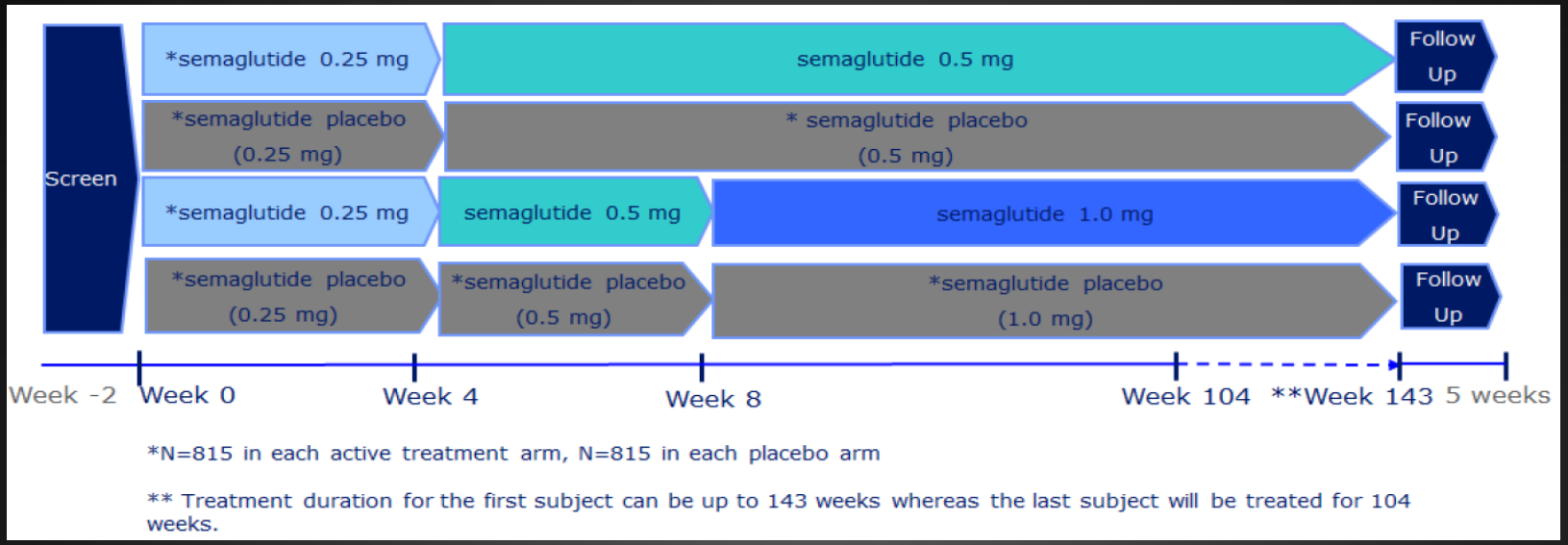
- Time from randomization to first occurrence of a composite CV outcome (CV death, non-fatal MI, or non-fatal stroke)

Key secondary endpoints

- Time from randomization to first occurrence of an expanded composite CV outcome (CV death, non-fatal MI, non-fatal stroke, revascularization, unstable angina or hosp. for heart failure)
- Time from randomization to all cause death
- Time from randomization to each individual component of the expanded composite CV outcome

N Engl J Med 2016;375:311-22

SUSTAIN-6 trial



- Phase 3a randomized, double-blind, placebo-controlled, parallel-group study
- Patients were randomized in a 1:1:1:1 ratio(826:822:824:825)
- Outcomes;

  Primary composite: 3 points MACE

  Secondary & Others

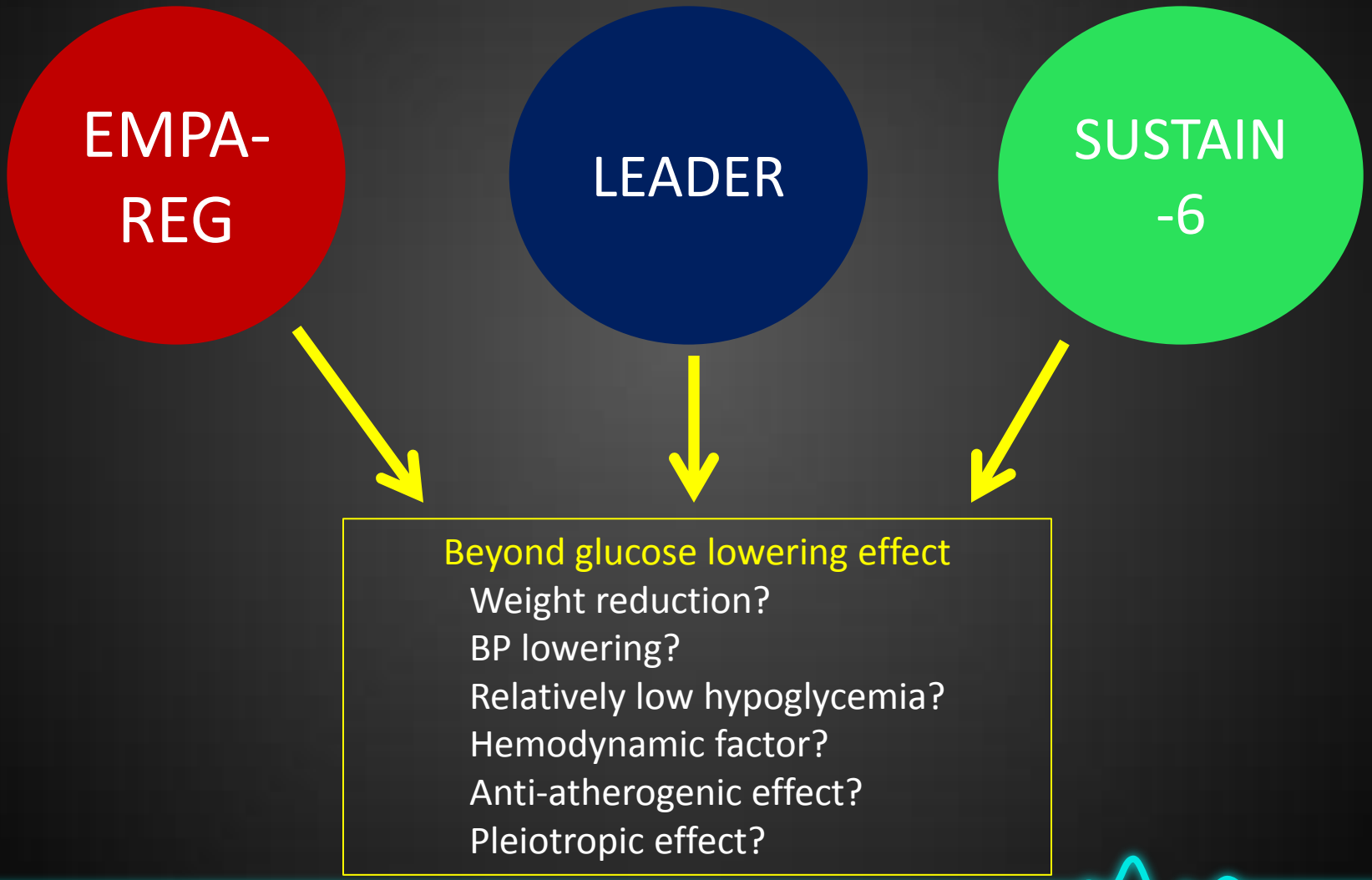
  - Primary + hospitalization for unstable angina or HF or + coronary revascularization
  - retinopathy complications
  - New or worsening nephropathy

N Engl J Med. 2016 Sep 15. [Epub ahead of print]

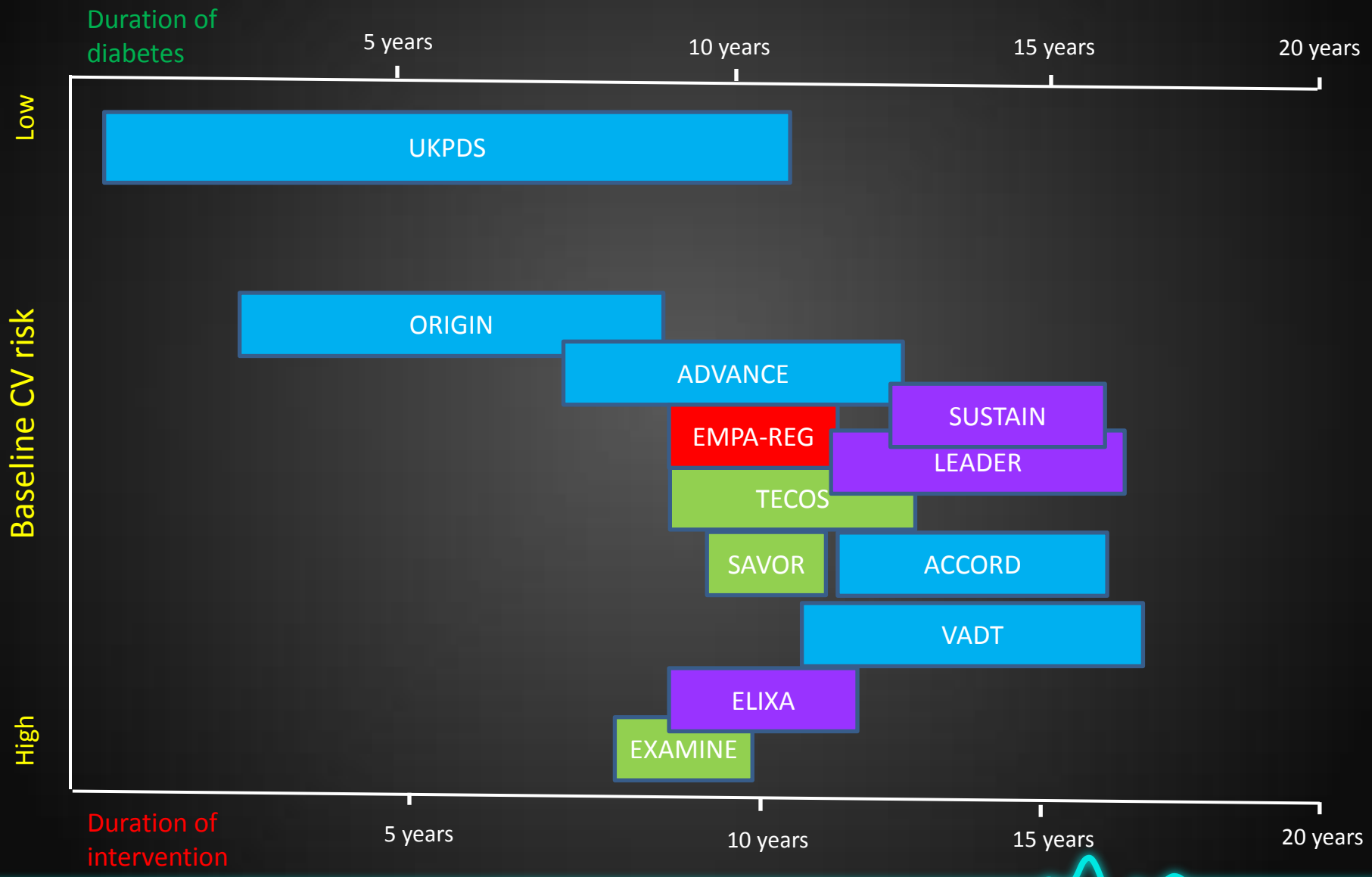
Comparisons of three benefit trials

	EMPA-REG	LEADER	SUSTAIN-6
Subject No.	7,028	9,340	3,297
Mean duration of diabetes	> 10 years(57 %)	12.8	14.0
Baseline HbA1c(%)	8.07	8.7	8.7
HbA1c change in investigating drug	-0.24 % in 10 mg -0.36 % in 25 mg	-0.4 %	-1.1 % in 0.5 mg -1.4 % in 1.0 mg
Baseline BMI	30.6	32.5	32.8
Weight reduction	-1.8 kg in 10 mg -2.7 kg in 25mg	-2.3 kg	-3.6 kg in 0.5 mg -4.9 kg in 1.0 mg
Median duration of study	2.6	3.8	2.1
Primary outcome	14% ↓	13% ↓	26% ↓
CV death	38% ↓	22% ↓	2% ↓
Non-fatal MI	13% ↓(excl. silent MI) 28% ↑ silent MI	12% ↓ 14% ↓ (incl. all MI)	26% ↓(incl. silent MI)
Non-fatal stroke	24% ↑	11% ↓	39% ↓
All-cause mortality	32% ↓	15% ↓	5% ↑
Hospitalization for HF	35% ↓	13% ↓	11% ↑
Time to benefit	within 3months	12-18 months	12-18 months

Recent three benefit trials



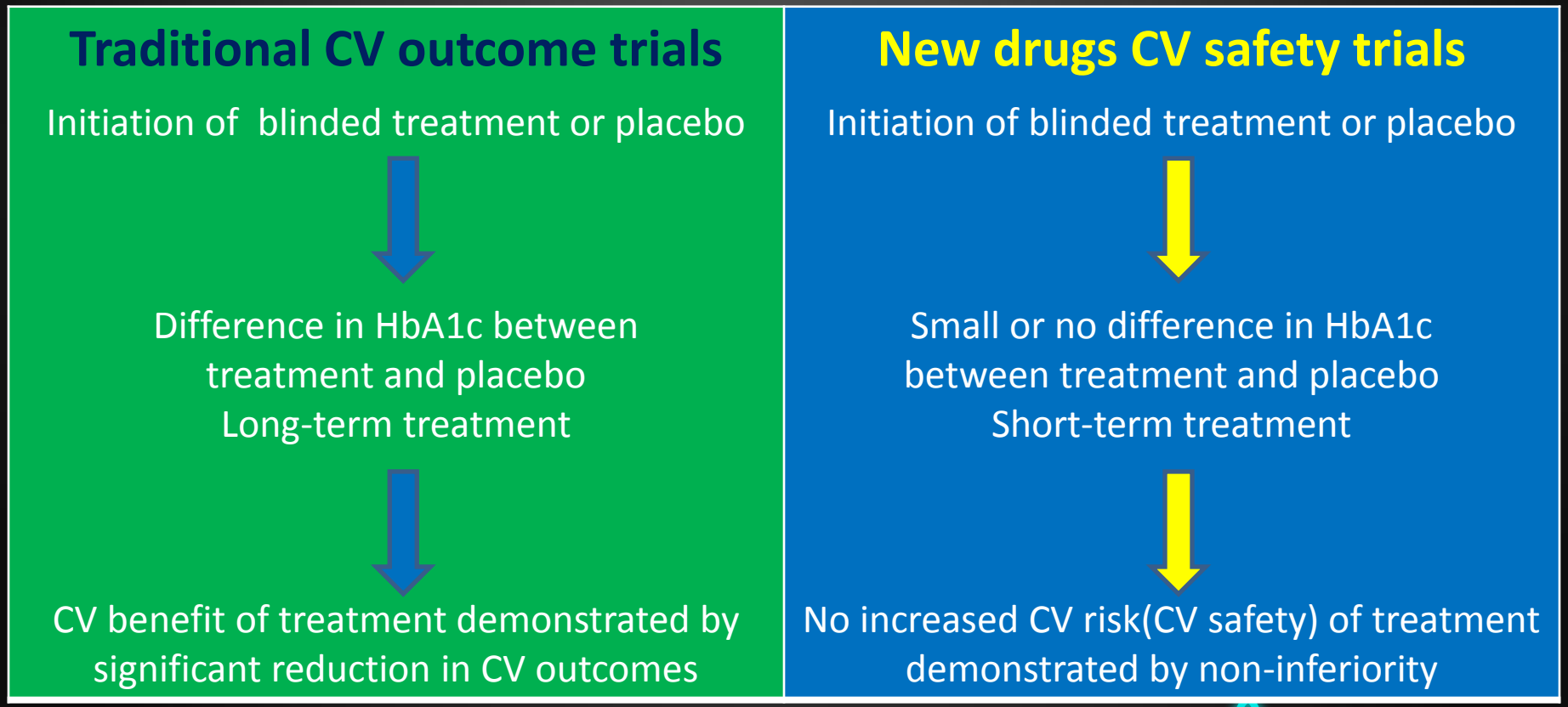
CVOT according to the duration of diabetes, baseline CV risk, and duration of intervention



Modified figure from World J Diabetes 2015; 6(9): 1092-1096

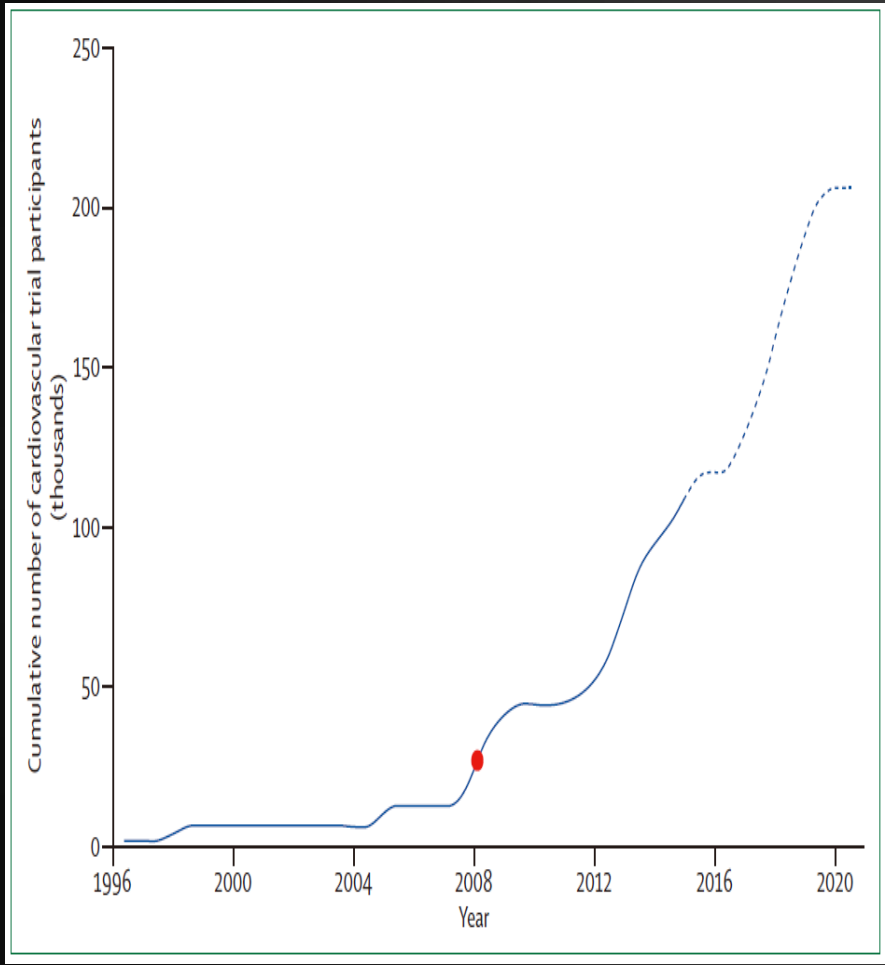
Potential limitations of CV outcome trial for New drug

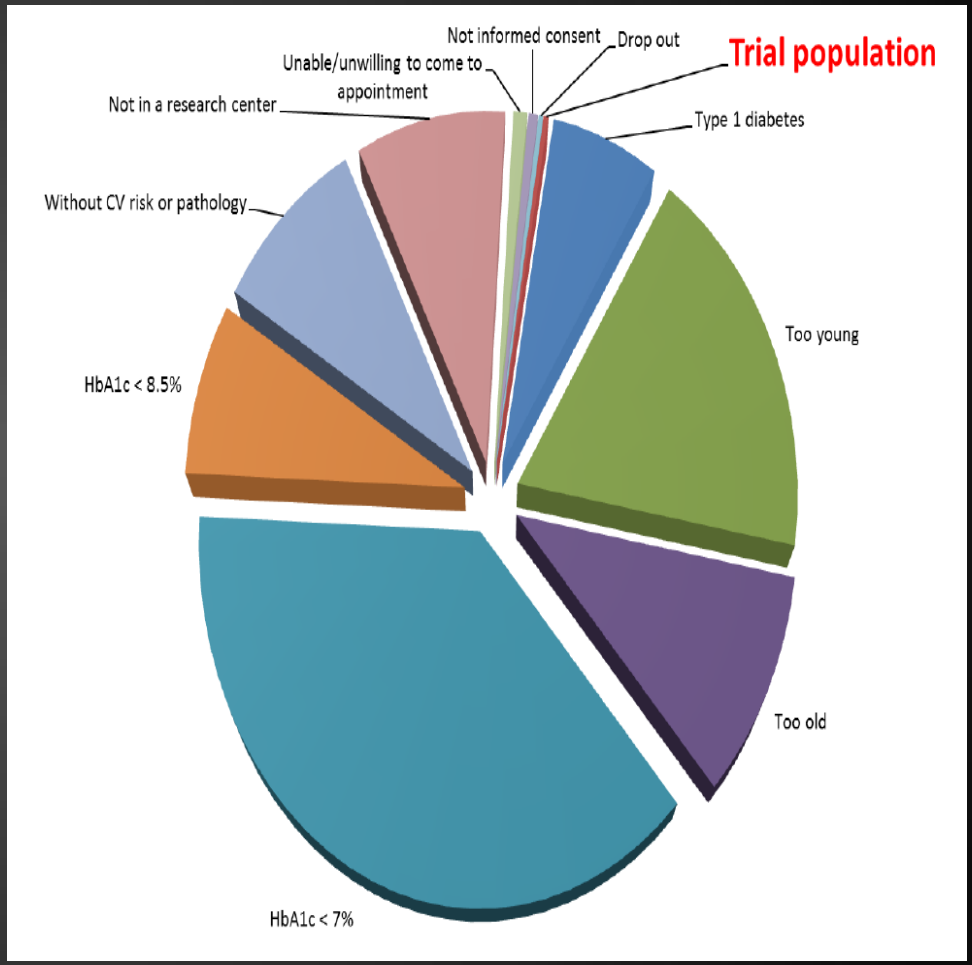
Traditional CV outcome trials :
Demonstrate CV benefit (lower CV risk vs placebo or active comparator)
New drugs CV safety trials :
Demonstrate CV safety (no increased CV risk vs placebo as part of standard care)



N Eng J Med 2013;369:1317-26, Am Heart J 2013;166:983-989

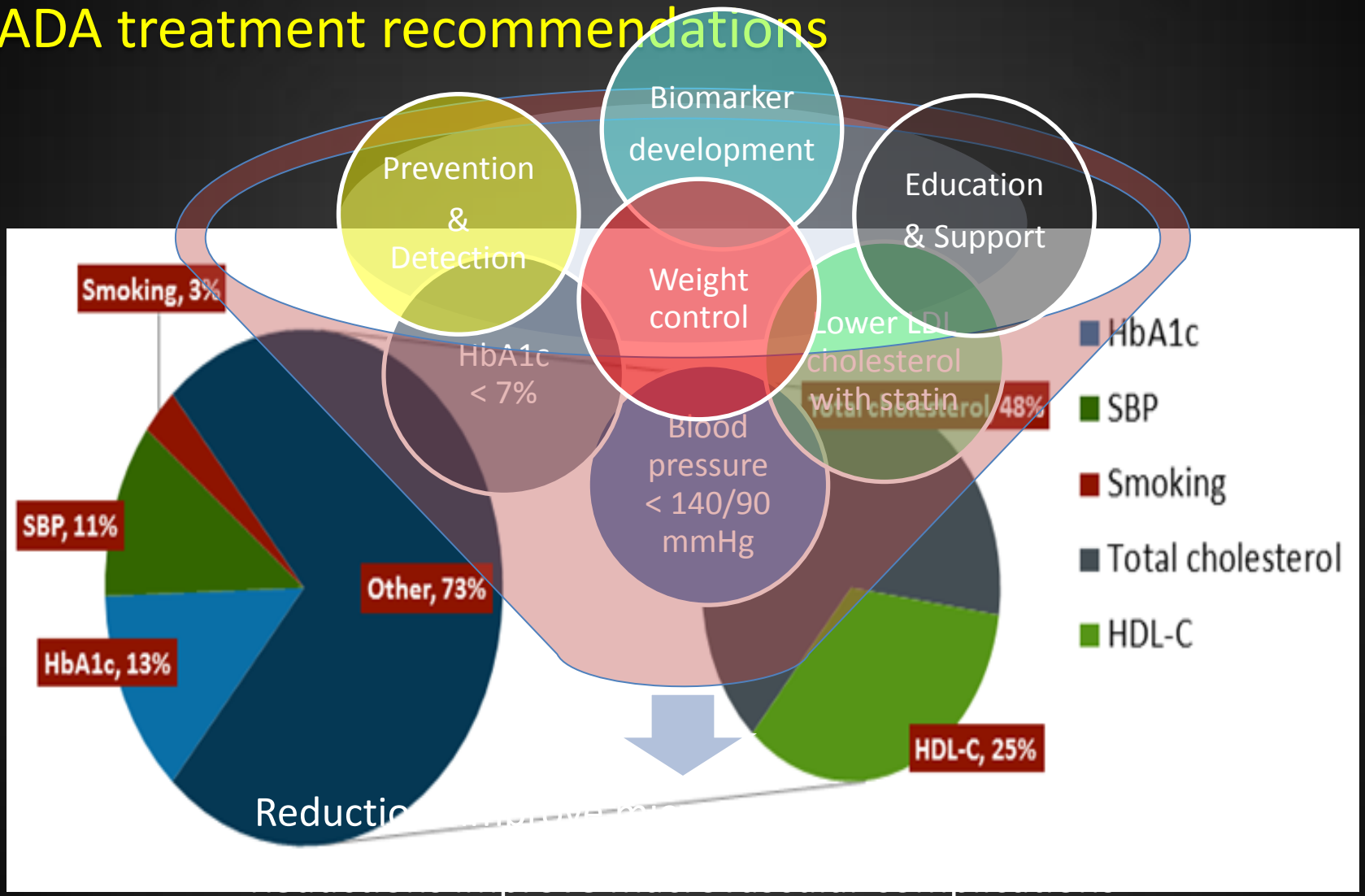
Trial include “Limited Population”





Metabolic Component of Diabetes

ADA treatment recommendations



ADA. Diabetes Care. 2016;39 Suppl 1:S1-S112

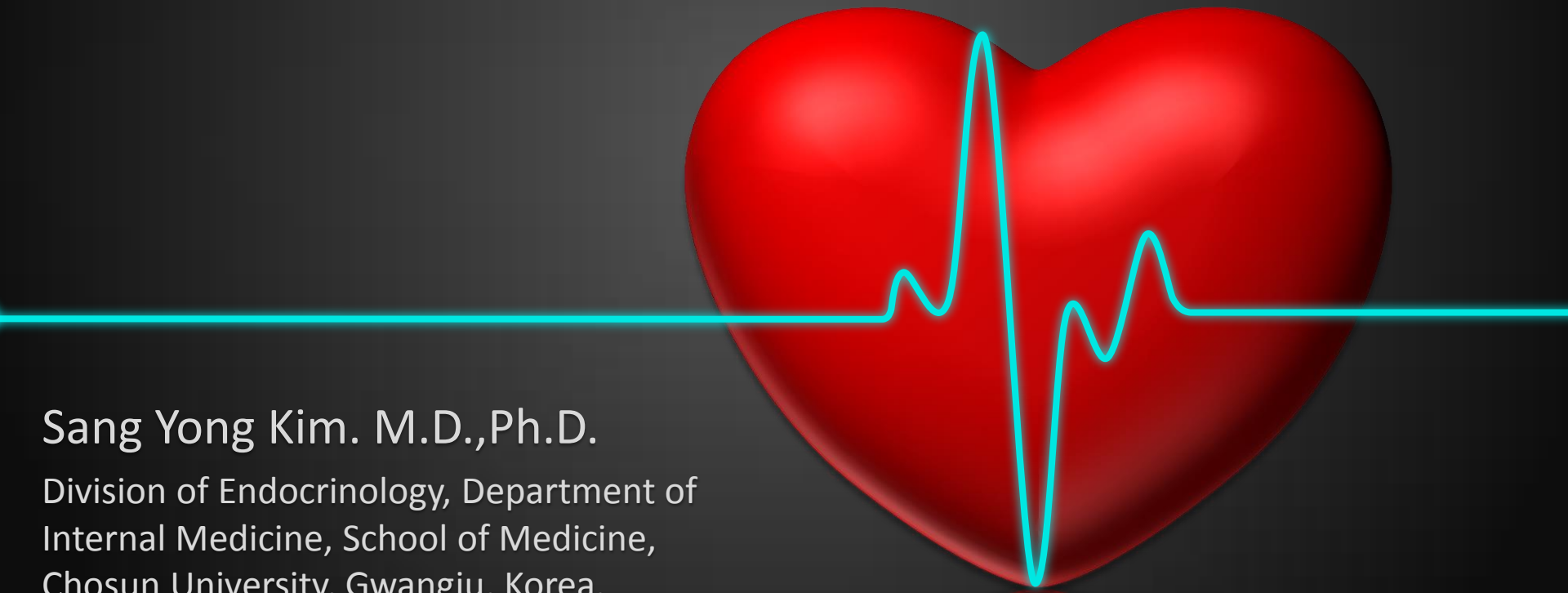
What can we learn from these large clinical trials of glycemic control for the cardiovascular disease?

Today's summary

Lesson from large clinical trials

- Traditional CV outcome trials showed that cardiovascular protective effect by intensive glycemic control can be achieved after long-term follow-up.
- It takes long time to show the benefits of intensive glycemic control for the reduction of cardiovascular disease in diabetic patients.
- It has become clear that recent CV outcome studies can rule out harm but have been too short to evaluate for a beneficial effect of strict glycemic control.
- EMPA-REG, LEADER, and SUSTAIN-6 trials demonstrated the beneficial effects for CVD, however, It is unlikely that benefits are solely from glucose-lowering effect.
- And also, these CV benefits can't be generalized to all diabetic patients and we need to observe how to translate into the real clinical practice.
- The pathophysiology of CVD in diabetic patients is very complex and multifactorial, we need to make a more exact risk stratification and appropriate strategies according to the individual characteristics.

Thanks for your attention!!



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