8th Annual Emirates Cardiac Society Conference

ACC Middle East Conference 2017

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The New Diabetes Drugs and Cardiovascular Outcomes

Bassam Atallah, PharmD, MS, BCPS-AQ Cardiology
Pharmacotherapy Specialist

Cleveland Clinic Abu Dhabi

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2008 FDA Requirements

- In 2008, FDA provided guidance for developing drug and therapeutic biologics for the treatment of DM
- A minimum of 2 years safety data from clinical studies
- To demonstrate no increase in CV risk using the MACE (Major Adverse Cardiac Events) endpoint
- Need to include CV death, MI and stroke data

U.S. Food and Drug Administration. 2008. Guidance for Industry – Diabetes Mellitus

DPP-4 Inhibitors

Trial	No. of Patients	Population	Drug	Median Follow-up	Results vs. placebo
SAVOR-TIMI 53 Increased CHF Hospitalization (HR 1.27, P < 0.007)	16,492	Hx or at risk of CV events	Saxagliptin	2.1 years	CV death, nonfatal MI, or nonfatal stroke (7.3% vs 7.2%, NS)
EXAMINE Trend for Increased CHF Hospitalization (HR 1.07, P = NS)	5380	Acute MI or unstable angina requiring hospitalization	Alogliptin	18 months	CV death, nonfatal MI, or nonfatal stroke (11.3% vs 11.8%, NS)
TECOS NO Increased CHF Hospitalization (HR 1.00)	14,671	CV disease	Sitagliptin	3 years	CV death, nonfatal MI, nonfatal stroke or hospitalization for unstable angina (11.4% vs. 11.6%, NS)

N Engl J Med 2013;36:1317-26
Lancet. 2015;385:2067-76
N Engl J Med. 2015;373:232-42

Limitations to the DPP-4 Inhibitors Trials

- Heterogeneous study populations between trials
  - Baseline A1C
  - DM duration
  - Previous HF
- Different criteria and endpoints
- Meta-analyses driven by results from SAVOR-TIMI

Heart Failure

- SAVOR –TIMI 53 and EXAMINE both showed increased risk of HF
- SAVOR-TIMI 53 is the only one with statistically significant risk
- FDA warning regarding increased risk with saxagliptin and alogliptin but not sitagliptin

N Engl J Med. 2013;36:1317-26
Lancet. 2015;385:2067-76
N Engl J Med. 2015;373:232-42

FDA Drug Safety Communication: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin

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This is an update to the FDA Drug Safety Communication: FDA to review heart failure risk with diabetes drug saxagliptin (marketed as Onglyza and Kombiglyze XR) issued on February 11, 2014.

Safety Announcement

[4-5-2016] A U.S. Food and Drug Administration (FDA) safety review has found that type 2 diabetes medicines containing saxagliptin and alogliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease. Heart failure can result in the heart not being able to pump enough blood to meet the body's needs. As a result, we are adding new warnings to the drug labels about this safety issue.

https://www.fda.gov/Drugs/DrugSafety/ucm486096.htm

ELIXA Trial

- Lixisenatide in patients with type 2 diabetes and acute coronary syndrome
- Individuals who had a recent MI or had been hospitalized for unstable angina
- Composite primary endpoint: CV death, MI, stroke, or hospitalization for unstable angina
- Median follow-up period of 25 months

N Engl J Med 2015;373:2247-57

ELIXA Trial (Cont.)

- Primary outcome was not different between lixisenatide and placebo (13.2% vs 13.4%, HR 1.02, 95% CI, 0.89-1.17)
- No difference in HF or HF hospitalization
- Superiority not met:
  - Need for longer follow-up
  - Patients had advanced CV disease with preexisting atherosclerosis

N Engl J Med 2015;373:2247-57

LEADER Trial

- Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes
- Patients with history of, or at risk of, CV disease
- Composite primary endpoint: the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke
- Median follow-up period of 3.8 years

N Engl J Med. 2016;375:311-22

LEADER Trial (Cont.)

- The primary outcome occurred in significantly fewer patients in the liraglutide group
  - (608 of 4668 patients [13.0%]) than in the placebo group (694 of 4672 [14.9%]) (hazard ratio, 0.87; 95% confidence interval [CI], 0.78 to 0.97; P<0.001 for noninferiority; P = 0.01 for superiority)
- All components of the primary endpoint occurred less in the liraglutide group; however, only death from CV causes was significant (HR 0.78, 95% CI, 0.66-0.93)

N Engl J Med. 2016;375:311-22

FDA Grants Liraglutide Cardiovascular Events Indication

Miriam E. Tucker

DISCLOSURES | August 25, 2017

The US Food and Drug Administration (FDA) has approved a new indication for liraglutide (*Victoza*, Novo Nordisk), for reducing the risk for myocardial infarction, stroke, and cardiovascular death in adults with type 2 diabetes who have established cardiovascular disease.

Today's approval marks the second time a drug initially approved for glucose lowering in type 2 diabetes has gained an additional indication for cardiovascular benefit based on results from FDA-mandated cardiovascular outcomes trials. The first, empagliflozin (*Jardiance*, Boehringer Ingelheim

http://www.medscape.com/viewarticle/884726

SUSTAIN-6 Trial

- Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes
- Not yet FDA approved once weekly GLP-1 RA with an extended half-life
- Composite primary endpoint: the first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke
- Median follow-up period of 2.1 years

N Engl J Med 2016;375:1834-44.

SUSTAIN-6 Trial

- The primary outcome occurred less in the semaglutide group (HR 0.74; 95% CI, 0.58-0.95; p<0.001 for noninferiority, p=0.02 for superiority; NNT=45)
- All components of the primary endpoint occurred less in the semaglutide group; however, only nonfatal stroke was significant (HR 0.61, 95% CI, 0.38-0.99)

N Engl J Med 2016;375:1834-44.

EXSCEL Trial

- Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes
- Patients with type 2 diabetes, with or without previous cardiovascular disease, to receive subcutaneous injections of extended-release exenatide at a dose of 2 mg or matching placebo once weekly
- The primary composite outcome was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke
- Median follow-up period of 2.1 years

N Engl J Med 2017;377:1228-39.

EXSCEL Trial

- The primary composite outcome event occurred in 839 of 7356 patients (11.4%; 3.7 events per 100 person-years) in the exenatide group and in 905 of 7396 patients (12.2%; 4.0 events per 100 person-years) in the placebo group (hazard ratio, 0.91;95% confidence interval [CI], 0.83 to 1.00)
- Non-inferior but no superiority unlike in the LEADER trial

N Engl J Med 2017;377:1228-39.

EMPA-REG OUTCOME Trial

- Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes
- All the patients had established cardiovascular disease
- Composite primary endpoint: CV death, nonfatal MI, or nonfatal stroke
- Median follow-up period of 3.1 years

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

EMPA-REG OUTCOME Trial (Cont.)

- The primary outcome occurred in 10.5% in the empagliflozin group and 12.1% in the placebo group (hazard ratio in the empagliflozin group, 0.86; 95.02% confidence interval, 0.74 to 0.99; P = 0.04 for superiority)
- Benefit driven from death from CV causes
- Secondary end points in favor of empagliflozin included death from any cause (5.7% vs 8.3%, p<0.001) and hospitalization for HF (2.7% vs. 4.1%, p=0.002)
- Rapid separation in survival curves

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

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FDA News Release

FDA approves Jardiance to reduce cardiovascular death in adults with type 2 diabetes

Study links Jardiance to improved survival in patients with type 2 diabetes with cardiovascular disease

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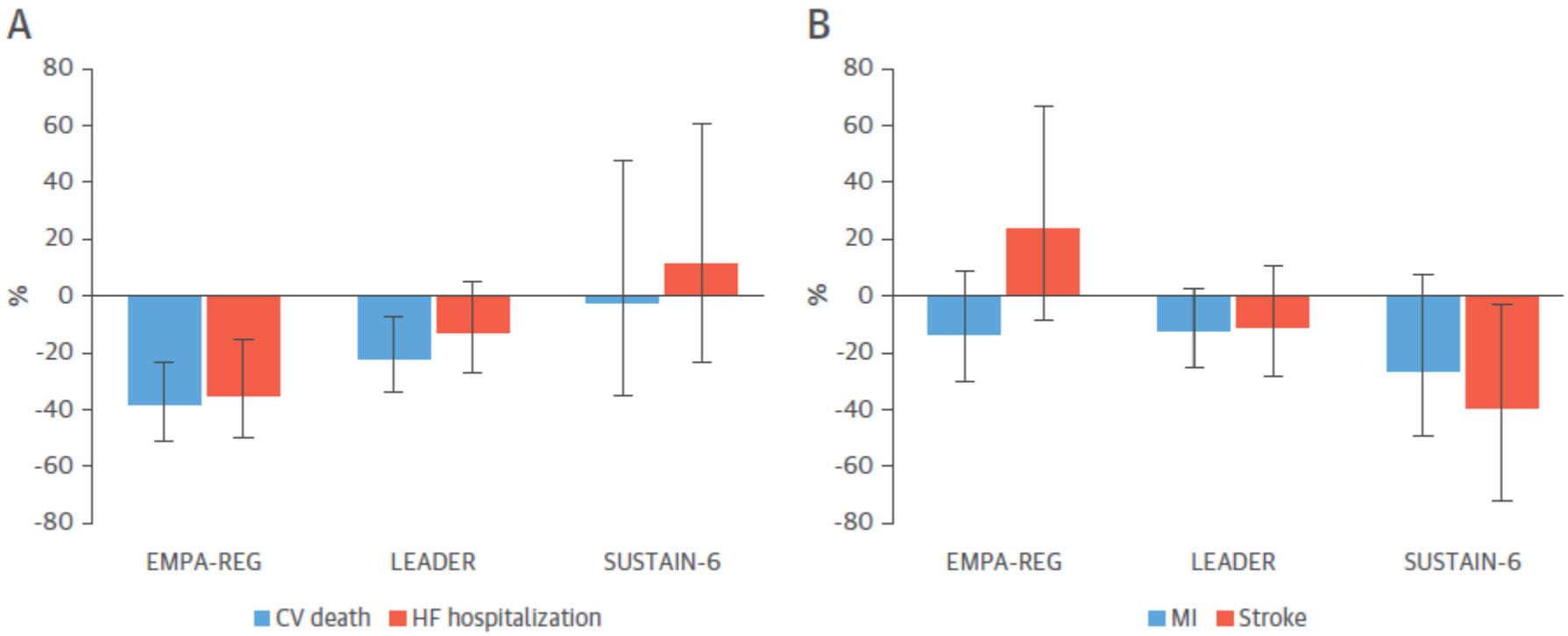
For Immediate Release December 2, 2016

https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm531517.htm

FIGURE 1 Comparing and Contrasting the Outcome Benefits in the EMPA-REG OUTCOME, LEADER, and SUSTAIN-6 Trials



[Figure 1] In *JACC*. 2017;69:2646-56

CANVAS trial

- Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes
- Patients with DM and high cardiovascular risk
- Composite primary outcome of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke
- Median follow-up period of 3.1 years

N Engl J Med. 2017; 3777:644-57

CANVAS trial (Cont.)

- The primary outcome was lower with canagliflozin than with placebo (occurring in 26.9 vs. 31.5 participants per 1000 patient-years; hazard ratio, 0.86; 95% confidence interval [CI], 0.75 to 0.97; P<0.001 for noninferiority;P = 0.02 for superiority)
- Secondary outcomes included a lower rate of progression of albuminuria but a higher rate of amputation

N Engl J Med. 2017; 3777:644-57

FDA Drug Safety Communication: FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR)

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7/2017 Update: The issues described below have been addressed in product labeling. Health care professionals and patients can access the approval letters and latest prescribing information by searching for canagliflozin at: **Drugs@FDA**

https://www.fda.gov/Drugs/DrugSafety/ucm557507.htm

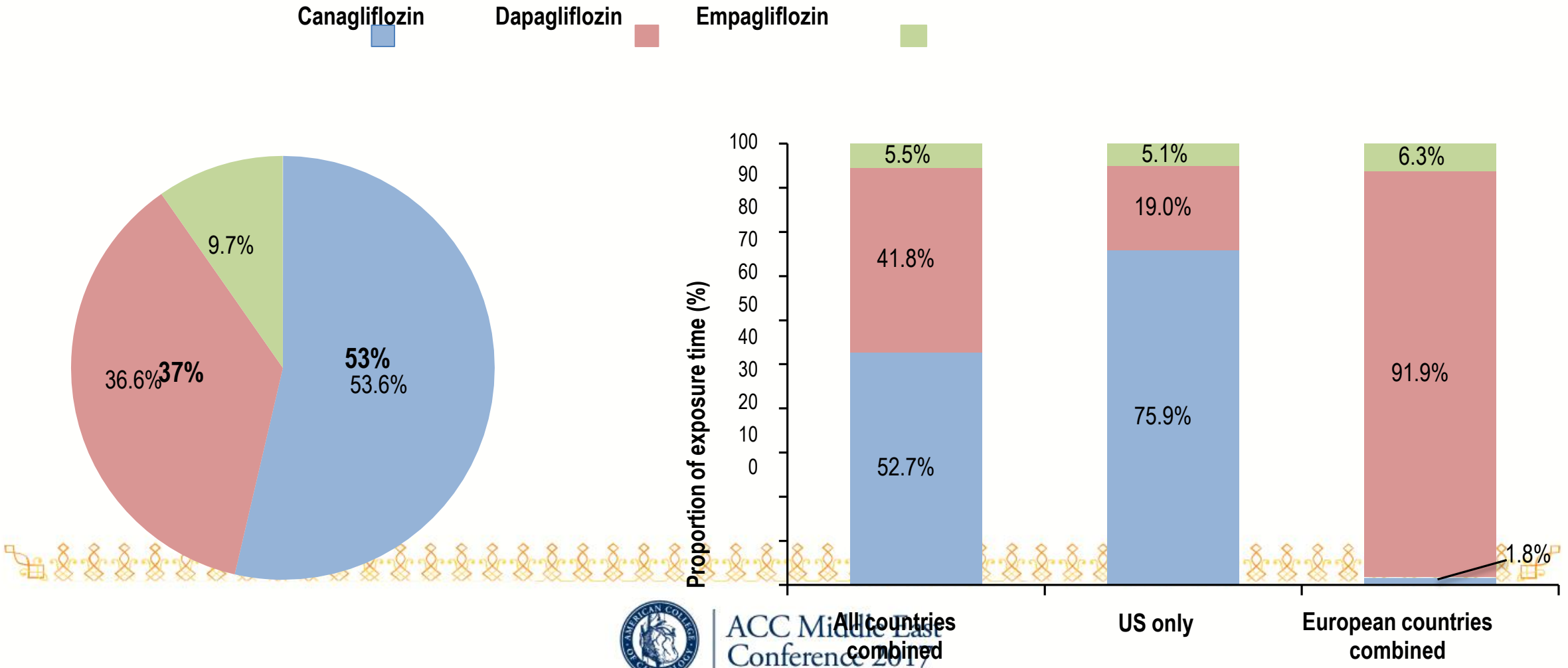
CVD-REAL Study

- Lower Risk of Heart Failure and Death in Patients Initiated on SGLT-2 Inhibitors Versus Other Glucose-Lowering Drugs
- Patients from six countries newly initiated on SGLT-2 inhibitors versus other glucose lowering drugs (oGLDs)
- Comparison of incidence of hospitalization for heart failure (HHF) and death
- Mean duration of follow up for HHF was 239 days in the SGLT-2i group and 211 days in the oGLD group

Circulation. 2017; DOI:CIRCULATIONAHA.117.029190

Contribution of SGLT-2 inhibitor Class as a Proportion of Exposure Time in Propensity-Match Cohorts

Cohort 1: HHF Analysis (N=309,046)



CVD-REAL Study (Cont.)

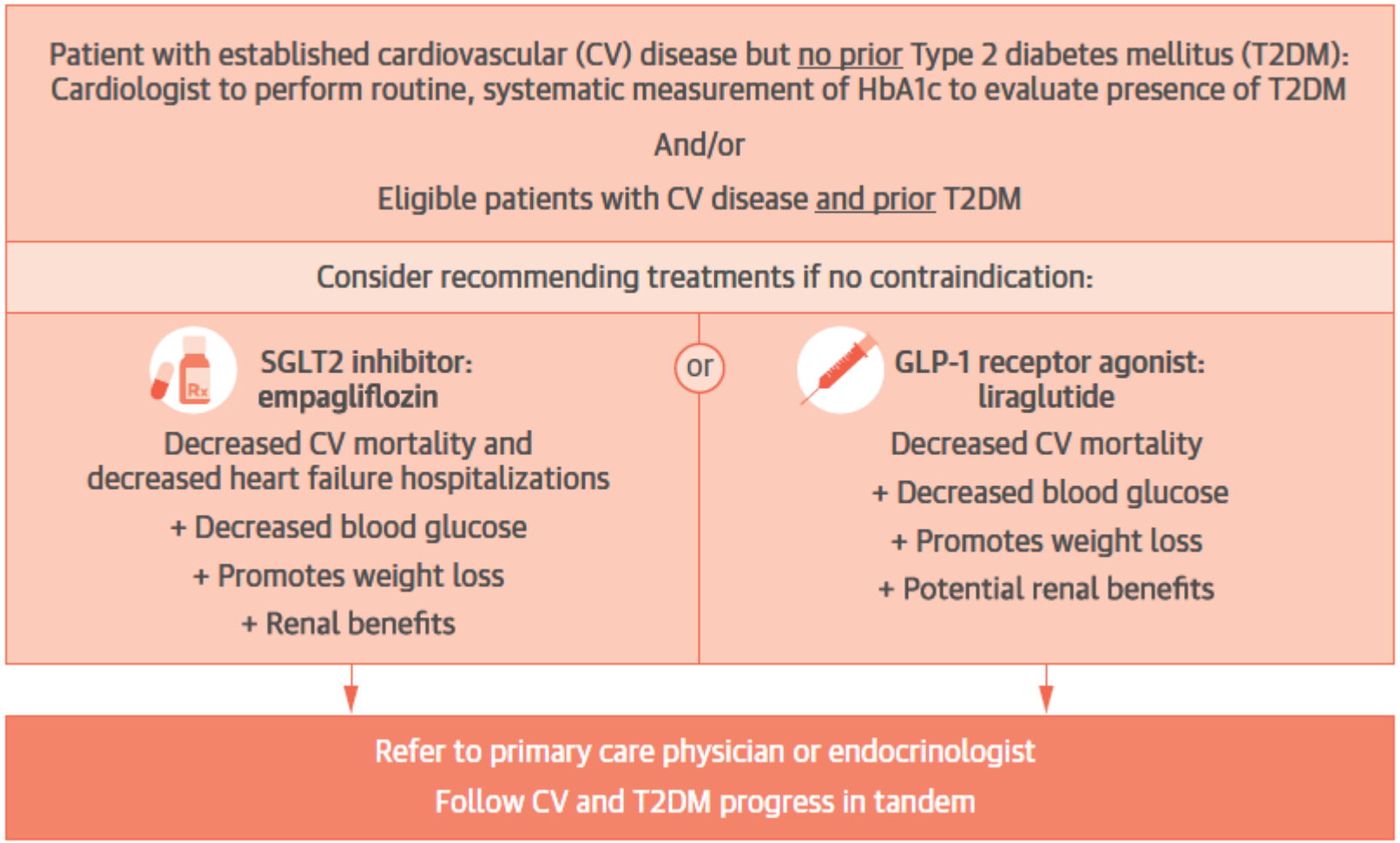
- Use of SGLT-2i, versus oGLDs, was associated with lower rates of HHF (HR 0.61; 95% CI 0.51–0.73; p<0.001); death (HR 0.49; 95% CI 0.41–0.57; p<0.001); and HHF or death (HR 0.54; 95% CI 0.48–0.60, p<0.001)
- Results consistent with the EMPA-REG study even though most patients were on other SGLT-2 inhibitors (53% canagliflozin, 42% dapagliflozin, 5% empagliflozin)
- **Approximately 87% of patients did not have known CVD (hinting at primary prevention role of CVD in DM patients?)**

Circulation. 2017; DOI:CIRCULATIONAHA.117.029190

Trials in Progress

- CARMELINA (linagliptin vs Pl)
- CAROLINA (linagliptin vs glimepiride)
- REWIND (dulaglutide vs Pl)

CENTRAL ILLUSTRATION Novel Paradigm for Care of the Patient With CV Disease and T2DM



Sattar, N. et al. J Am Coll Cardiol. 2017;69(21):2646-56.

Summary

- Cardiologists can improve detection of DM by performing routine HbA_{1c} measurements
- CV benefits may require long follow-up periods in trials
- Choice of add-on therapy for DM may be based on both CV safety and benefit and not just the glucose-lowering effect
- Consider empagliflozin and liraglutide particularly for those with history of established CVD
- Consider lowering loop diuretic dose when adding SGLT-2 inhibitor
- Head to head trials are needed to determine if CV risks and benefits of DM individual drugs can be assumed as a class effect

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