

# Updates in Diabetes and Cardiovascular Disease Management: Are You Making the Link?

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*The speakers have no actual or potential conflicts of interest in relation to this activity.*



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## Learning Objectives - Pharmacist

- Apply recent changes to blood pressure goals in patients with diabetes
- Assess the role of new antihyperglycemic therapies in preventing major adverse cardiovascular events
- Discuss the benefits, concerns, and barriers when incorporating new cardiovascular risk strategies in patients with diabetes



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## Cardiovascular Risk and Diseases in Diabetes

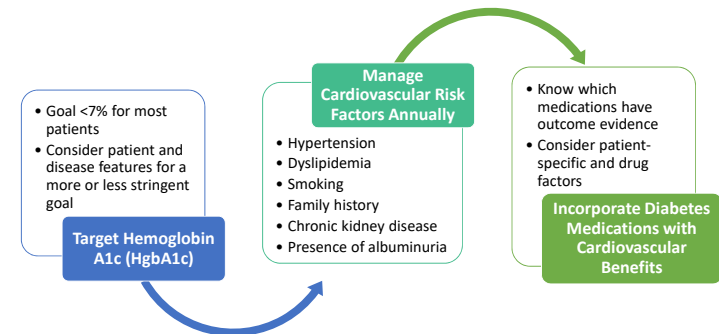
- Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality in a patient with diabetes mellitus (DM)
- Largest contributor to direct and indirect costs
- Hypertension (HTN) and dyslipidemia are clear risk factors for ASCVD in patients with diabetes



American Diabetes Association. Diabetes Care. 2018;41(Suppl 1):S73-S85.

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## Making the Link in Clinical Practice



American Diabetes Association. Diabetes Care. 2018;41(Suppl1):S55-S64.  
American Diabetes Association. Diabetes Care. 2018;41(Suppl1):S73-S85.

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## Hypertension and Diabetes

- Approximately 80% of adult DM patients have HTN
- Co-existence of HTN and DM significantly increases risk of:
  - Coronary heart disease
  - Stroke
  - Heart failure
  - Peripheral arterial disease
  - Cardiovascular mortality
  - Nephropathy
  - Retinopathy
- Limited quality evidence regarding optimal blood pressure goal in DM
- Many changes over recent years based on new evidence

Whelton PK, Carey RM, et al. *J Am Coll Cardiol.* 2018; 71(19):e127-e248.

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## Guideline Comparison of Blood Pressure Goals

| Guideline      | General HTN (mmHg) | Diabetes (mmHg)                   |
|----------------|--------------------|-----------------------------------|
| JNC7 (2003)    | <140/90            | <130/80                           |
| JNC8 (2014)    | <140/90            | <140/90                           |
| ADA (2014)     | N/A                | <140/80<br>(<130 if undue burden) |
| ADA (2015)     | N/A                | <140/90                           |
| ACC/AHA (2017) | <130/80            | <130/80                           |
| ADA (2018)     | N/A                | <140/90<br>(<130 if high CV risk) |

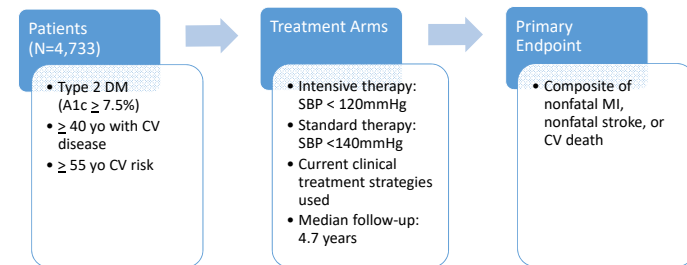
Chobanian AV, et al. *JAMA.* 2003; 289(19): 2560-71.  
 American Diabetes Association. *Diabetes Care.* 2014;37(Suppl. 1):S5-S13.  
 James PA, et al. *JAMA.* 2014; 311(5):507-520.  
 American Diabetes Association. *Diabetes Care.* 2015;38(Suppl. 1):S49-S57.  
 Whelton PK, et al. *J Am Coll Cardiol.* 2018; 71(19):e127-e248.  
 American Diabetes Association. *Diabetes Care.* 2018;41(Suppl. 1):S86-S104.



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## ACCORD BP

- The Action to Control Cardiovascular Risk in Diabetes blood pressure trial



CV= cardiovascular; MI= myocardial infarction; SBP= systolic blood pressure

The ACCORD Study Group. *N Engl J Med.* 2010; 362:1575-85.

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## ACCORD BP Results

- Patients: 62.2 years, 47.7% women, 33.7% CV disease
  - Baseline BP: 139.2/76 mmHg
- SBP at 1 year:
  - Intensive (119.3 mmHg) vs Standard (133.5 mmHg)

| Outcome         | Intensive Therapy<br>(N=2363)<br>N(%/year) | Standard Therapy<br>(N=2371)<br>N(%/year) | Hazard Ratio<br>(95% CI) | P Value |
|-----------------|--|---|--------------------------|---------|
| Primary*        | 208 (1.87)                                 | 237 (2.09)                                | 0.88 (0.73-1.06)         | 0.20    |
| Nonfatal MI     | 126 (1.13)                                 | 146 (1.28)                                | 0.87(0.68-1.10)          | 0.25    |
| Any Stroke      | 36 (0.32)                                  | 62 (0.53)                                 | 0.59 (0.39-0.89)         | 0.01    |
| Nonfatal Stroke | 34 (0.30)                                  | 55 (0.47)                                 | 0.63 (0.41-0.96)         | 0.03    |
| CV Death        | 60 (0.52)                                  | 58 (0.49)                                 | 1.06 (0.74-1.52)         | 0.74    |

The ACCORD Study Group. *N Engl J Med.* 2010; 362:1575-85.

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## 2018 ADA Recommendations

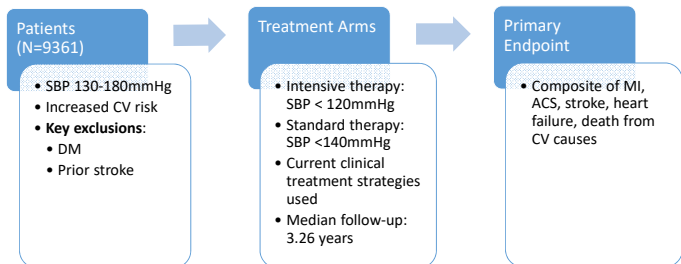
- At a minimum, treat to <140/90 mmHg to reduce CV and microvascular complications
- Lower goals (<130/80 or <120/80) may be beneficial if high CV risk
  - History of stroke
  - CV disease
  - Albuminuria
- Treatment goals should be individualized
- Pharmacologic treatment based on presence of albuminuria (>30mg/g)
  - Albuminuria: ACEi or ARB
  - Without albuminuria: ACEi, ARB, thiazide, calcium channel blocker
    - Proven reduction in CV events in DM patients

American Diabetes Association. *Diabetes Care.* 2018;41(Suppl. 1):S86-S104.

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## SPRINT

- A Randomized Trial of Intensive versus Standard Blood-Pressure Control



ACS= acute coronary syndrome; CV= cardiovascular; MI= myocardial infarction; SBP= systolic blood pressure

The SPRINT Research Group. *N Engl J Med.* 2015;373:2103-2116.

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## SPRINT Results

- Patients: 67.9 years, ~35% women, 20% CV disease
  - Baseline BP: 139.7/78 mmHg
- SBP at 1 year:
  - Intensive (121.4 mmHg) vs Standard (136.2 mmHg)

| Outcome         | Intensive Therapy<br>(N=4678)<br>N(%/year) | Standard Therapy<br>(N=4683)<br>N(%/year) | Hazard Ratio<br>(95% CI) | P Value |
|-----------------|--|---|--------------------------|---------|
| Primary*        | 243 (1.65)                                 | 319 (2.19)                                | 0.75 (0.64-0.89)         | <0.001  |
| MI              | 97 (0.65)                                  | 116 (0.78)                                | 0.83 (0.64-1.09)         | 0.19    |
| ACS             | 40 (0.27)                                  | 40 (0.27)                                 | 1.00 (0.64-1.55)         | 0.99    |
| Heart Failure   | 62 (0.41)                                  | 100 (0.67)                                | 0.62 (0.45-0.84)         | 0.002   |
| CV Death        | 37 (0.25)                                  | 65 (0.43)                                 | 0.57 (0.38-0.85)         | 0.005   |
| All Cause Death | 155 (1.03)                                 | 210 (1.40)                                | 0.73 (0.60-0.90)         | 0.003   |

The SPRINT Research Group. *N Engl J Med.* 2015;373:2103-2116.

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## 2017 ACC/AHA Recommendations

- Endorse lower BP goals based on SPRINT data
  - Known CVD or 10-year ASCVD risk  $\geq 10\%$ 
    - $<130/80$  mmHg
- Assumes vast majority of patients with DM have 10-year ASCVD risk of  $\geq 10\%$
- Reinforce that ACCORD was underpowered due to lower than expected event rates
- SPRINT sub-study showed patients with prediabetes had similar benefit than those with normoglycemia

Whelton PK, et al. *J Am Coll Cardiol*. 2018; 71(19):e127-e248.

## Summary

- Limited quality evidence available to determine optimal BP target in adults with DM
- Treatment goals should be individualized
- Goal  $<130/80$  mmHg if high risk and tolerated

## Patient Case: Meet SN

A 56-year-old male presents for a follow-up appointment in a pharmacist's diabetes clinic. Upon questioning, he reports taking his medications daily and has no side effects to report. He has a blood glucose log with him which reveals readings  $> 200$  over the past couple of months. He denies symptoms of hypoglycemia.

| Past Medical History  | Current Medications   | Social History   | Family History  |
|---|---|--|---|
| Type 2 diabetes mellitus<br>Hypertension<br>Hyperlipidemia<br>Peripheral vascular disease | Lisinopril 5 mg PO daily<br>Metformin 1000 mg PO BID<br>Atorvastatin 20 mg PO daily | Former smoker<br>Denies alcohol<br>Denies illicit substances | Father: alive, history of heart disease<br>Mother: died from stroke complications |

## Patient Case: Question #1

You assess SN's vitals which were taken at the beginning of his clinic appointment. His BP is 148/86, P 78, RR 14, and T 37.8 °C

According to the 2017 ACC and ADA guidelines, which of the following blood pressure goals is best to target in this patient?

- $< 120/80$  mmHg
- $< 130/80$  mmHg
- $< 140/90$  mmHg
- $< 150/90$  mmHg

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## 2008 FDA Guidance for Cardiovascular Risk

- New therapies must not result in an unacceptable increase in CV risk
- Inclusion of major CV events as endpoints in all phase 2 and 3 trials
  - Major CV events (**MACE**): death from CV causes, nonfatal myocardial infarction and nonfatal stroke
- Include high-risk patients for a meaningful estimate of CV risk
- Compare incidence of important CV events occurring with investigational agent versus control group



U.S. Food and Drug Administration. Guidance for Industry, Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. December 2008. Available from <https://www.fda.gov/downloads/Drugs/Guidances/ucm071627.pdf>. Accessed 16 July 2018.

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## 2008 FDA Guidance for CV Risk

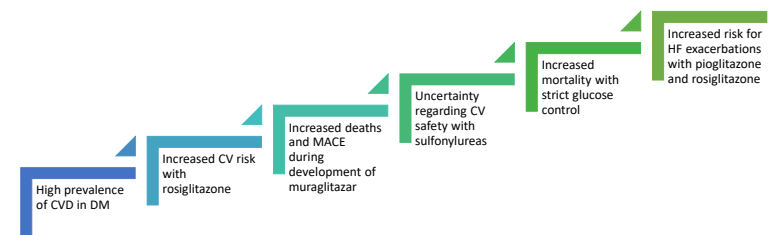
| Upper Bound of Two-Sided 95% Confidence Interval for Estimated CV Risk Ratio (investigational drug vs. control) |   |
|---|---|
| > 1.8   | <b>Decision:</b> Approval denied<br><b>Next Steps:</b> Additional, large safety trials should be conducted  |
| 1.3-1.8   | <b>Decision:</b> Approval granted as overall risk-benefit analysis supports approval<br><b>Next Steps:</b> Postmarketing trial generally necessary to definitely show estimated risk ratio is < 1.3 |
| < 1.3   | <b>Decision:</b> Approval granted as overall risk-benefit analysis supports approval<br><b>Next Steps:</b> Postmarketing trial may not be necessary   |



U.S. Food and Drug Administration. Guidance for Industry, Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. December 2008. Available from <https://www.fda.gov/downloads/Drugs/Guidances/ucm071627.pdf>. Accessed 16 July 2018.

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## Why was the guidance created?



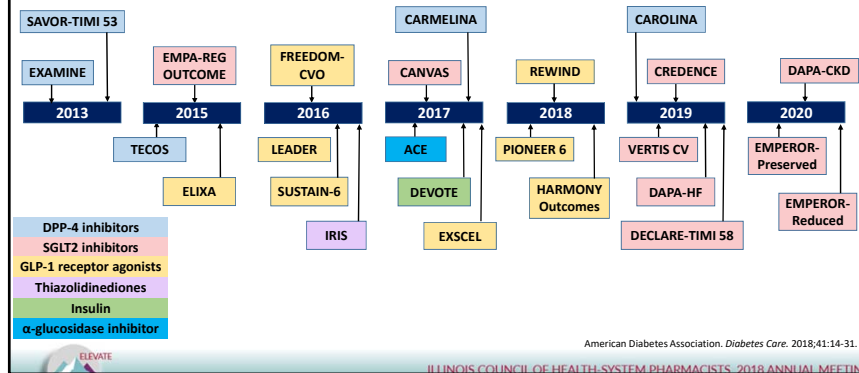
CVD= cardiovascular disease; HF= heart failure

Smith RJ et al. Diabetes Care. 2016;39:738-42.



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## Timeline of CV Outcome Trials in T2DM



## DPP-4 Inhibitors: Summary of CV Risk Trials

| Medication/Trial   | Saxagliptin / SAVOR-TIMI-53  | Alogliptin / EXAMINE   | Sitagliptin / TECOS   |
|--|--|--|---|
| <b>Control Arm</b>   | Placebo  | Placebo  | Placebo   |
| <b>Design</b>  | Randomized, DB, PC<br>788 sites, 26 countries<br>16,492 patients                               | Randomized, DB<br>898 sites, 49 countries<br>5380 patients                   | Randomized, DB, PC<br>673 sites, 38 countries<br>14,735 patients                          |
| <b>Type 2 Diabetes Mellitus (T2DM) Population</b>  | HgbA1c 6.5-12% (mean, 8%)<br>History of CVD (78%) OR multiple risk factors for CVD             | HgbA1c 6.5-11% (mean, 8%)<br>- If on insulin: 7-11%<br>ACS within 15-90 days | Age 50+<br>HgbA1c 6.5-8% (mean, 7.2%)<br>History of CVD                                   |
| <b>Primary Composite Endpoint &amp; Results</b>  | MACE = not significant (NS)  | MACE= NS   | MACE <b>plus</b> hospitalization for UA<br>- Per-protocol: SS<br>- Intention-to-treat: NS |
| <b>Secondary Composite Endpoint &amp; Results</b>  | Primary composite <b>PLUS</b> , hospitalization for UA, HF, or coronary revascularization = NS | Primary composite <b>PLUS</b> , urgent revascularization due to UA = NS      | MACE, per-protocol: SS<br>MACE, intention-to-treat: NS                                    |
| <b>Other Notes</b>   | Hospitalization for HF $\uparrow$ (HR 1.27)  | Non-significant trend in $\uparrow$ HF                                       | None  |
| <b>DPP-4 inhibitors do not have a FDA approved indication to reduce CV mortality and events in patients with T2DM and ASCVD.</b> |  |  |   |

Source: Scirica BM et al. NEJM. 2013;369:1317-26. White WB et al. NEJM. 2013;369:1327-35. Green JB et al. NEJM. 2015;373:232-42.

## SGLT-2 Inhibitors: Summary of CV Risk Trials

| Medication  | Empagliflozin   | Canagliflozin   | Danagliflozin  |
|---|---|---|--|
| <b>Trial Name</b>   | EMPA-REG  | CANVAS  | DECLARE-TIMI-58  |
| <b>Control Arm</b>  | Placebo   | Placebo   | Placebo  |
| <b>Design</b>   | Randomized, DB, PC<br>590 sites, 42 countries<br>7028 patients  | Randomized, DB, Parallel, PC<br>667 sites, 30 countries<br>10,142 patients  | Randomized, DB, PC<br>882 sites, 33 countries<br>17,160 patients   |
| <b>T2DM Population</b>  | HgbA1c ranges:<br>- If no Rx: 7-9%<br>- If stable Rx: 7-10%<br>Established ASCVD<br>BMI $\leq$ 45 kg/m <sup>2</sup><br>eGFR $\geq$ 30 ml/min/1.73m <sup>2</sup> | HgbA1c 7-10.5%<br>Age $\geq$ 30 with established ASCVD<br><b>OR</b><br>Age $\geq$ 50 with $\geq$ 2 CVD risk factors<br>eGFR $\geq$ 30 ml/min/1.73m <sup>2</sup> | HgbA1c 6.5 to $<$ 12%<br>Age $\geq$ 40 with established ASCVD <b>OR</b> $\geq$ 2 CVD risk factors<br><b>OR</b><br>Male $\geq$ 55, Female $\geq$ 60 with 1 risk factor<br>CrCl $\geq$ 60 mL/min |
| <b>All trials had a primary composite endpoint of death from CV causes, nonfatal myocardial infarction, and nonfatal stroke</b> |   |   |  |
| <b>Secondary Composite Endpoint</b>   | Primary composite <b>PLUS</b> hospitalization for UA  | Not applicable  | Primary composite <b>PLUS</b> CV death/hospitalization for HF  |
| <b>Duration</b>   | 2.6 years   | 188.2 weeks (total study: 8 yrs)  | Estimated Completion: 7/18/18  |

BMI= body mass index; CrCl= creatinine clearance;  
eGFR= estimated glomerular filtration rate

Zinman B et al. NEJM. 2015;373(22):2117-28.  
Neal B et al. NEJM. 2017;377(7):644-57.  
Wiviott SD et al. American Heart Journal. 2018;200:83-89.

## SGLT-2 Inhibitors: Baseline Demographics

|  | Empagliflozin / EMPA-REG  | Canagliflozin / CANVAS |
|--|---|------------------------|
| <b>Age (mean-yrs)</b>                  | 63.1  | 63.3                   |
| <b>Duration of Diabetes</b>            | $\leq$ 1 year: 2.45%<br>>1-5 years: 15.55%<br>5-10 years: 24.8%<br>>10 years: 57.2% | 13.5 (median-yrs)      |
| <b>Baseline HgbA1c (mean)</b>          | 8.08  | 8.2                    |
| <b>Established ASCVD – %</b>           | 99  | 56                     |
| <b>Hypertension – %</b>                | NR  | 90                     |
| <b>Prior HF – %</b>                    | NR  | 14.4                   |
| <b>Current smoker</b>                  | NR  | 17.8                   |
| <b>BMI – kg/m<sup>2</sup></b>          | 30.7  | 32                     |
| <b>eGFR – ml/min/1.73m<sup>2</sup></b> | 74  | 76.5                   |

Zinman B et al. NEJM. 2015;373(22):2117-28.  
Neal B et al. NEJM. 2017;377(7):644-57.

## SGLT-2 Inhibitors: Results

|                                 | Empagliflozin / EMPA-REG                   |                   | Canagliflozin / CANVAS   |                   |
|---------------------------------|--|-------------------|--|-------------------|
|                                 | HR (95%CI)                                 | P Value           | HR (95%CI)   | P Value           |
| <b>Primary Composite</b>        | 0.86 (0.74-0.99)                           | <0.001*<br>0.04^^ | 0.86 (0.75-0.97)   | <0.001*<br>0.02^^ |
| <b>Secondary Composite</b>      | 0.89 (0.78-1.01)                           | <0.001*<br>0.08^^ | NA   | NA                |
| <b>Death from CV causes</b>     | 0.62 (0.49-0.77)                           | <0.001            | 0.87 (0.72-1.06)   | 0.24              |
| <b>Nonfatal MI</b>              | 0.87 (0.70-1.09)                           | 0.23              | 0.85 (0.69-1.05)   | --                |
| <b>Nonfatal stroke</b>          | 1.24 (0.92-1.67)                           | 0.16              | 0.90 (0.71-1.15)   | --                |
| <b>Death from any cause</b>     | 0.68 (0.57-0.82)                           | <0.001            | 0.87 (0.74-1.01)   | 0.24              |
| <b>Hospitalization for HF</b>   | 0.65 (0.50-0.85)                           | 0.002             | 0.67 (0.52-0.87)   | --                |
| <b>Other Study Notes</b>        | ↓ progression of renal disease (p < 0.001) |                   | ↑↑ risk of amputation (HR 1.97)<br>↑ fracture risk (HR 1.26)<br>↓ progression of renal disease (p < 0.001) |                   |
| <b>FDA Approved Indication?</b> | YES  |                   | NO   |                   |

Zinman B et al. *NEJM*. 2015;373(22):2117-28.  
Neal B et al. *NEJM*. 2017;377(7):644-57.

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## GLP-1 Agonists: Summary of CV Risk Trials

| Medication                             | Lixisenatide  | Liraglutide  | Semaglutide  | Exenatide   |
|--|---|--|--|---|
| <b>Trial Name</b>                      | <b>ELIXA</b>  | <b>LEADER</b>  | <b>SUSTAIN-6</b>   | <b>EXSCEL</b>   |
| <b>Control Arm</b>                     | Placebo   | Placebo  | Placebo  | Placebo   |
| <b>Design</b>                          | Randomized, DB, PC<br>49 countries<br>6068 patients   | Randomized, DB, PC<br>410 sites, 32 countries<br>9340 patients                         | Randomized, DB, PC, PG<br>230 sites, 20 countries<br>3297 patients                     | Randomized, DB, PC<br>687 sites, 35 countries<br>14,752 patients                |
| <b>T2DM Population</b>                 | ACS event within 180 days   | HgbA1c ≥7%<br>Age ≥50 + ≥1 CVD <b>OR</b><br>Age ≥60 + ≥1 CV risk factor                | HgbA1c ≥7%<br>Age ≥50 + ≥1 CVD <b>OR</b><br>Age ≥60 + ≥1 CV risk factor                | HgbA1c 6.5-10%<br>Any level of CV risk<br>- 30% no CV events<br>- 70% CV events |
| <b>Primary Composite Endpoint</b>      | CV death, nonfatal MI, nonfatal stroke, UA  | CV death, nonfatal MI, nonfatal stroke   | CV death, nonfatal MI, nonfatal stroke   | CV death, nonfatal MI, nonfatal stroke  |
| <b>Secondary Composite Endpoint(s)</b> | 1. Primary composite or hospitalization for HF<br>2. Above <b>PLUS</b> coronary revascularization | Primary composite <b>PLUS</b> coronary revascularization, hospitalization for UA or HF | Primary composite <b>PLUS</b> coronary revascularization, hospitalization for UA or HF | <i>Not applicable</i>   |
| <b>Duration</b>                        | 25 months   | 3.8 years  | 2.1 years  | 3.2 years   |

Pfeiffer MA et al. *NEJM*. 2015;373(23):2247-57.  
Marso SP et al. *NEJM*. 2016;375(4):311-22.  
Holman RR et al. *NEJM*. 2017;377(13):1228-39.

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## GLP-1 Agonists: Baseline Demographics

|  | Lixisenatide / ELIXA | Liraglutide / LEADER | Semaglutide / SUSTAIN-6 | Exenatide / EXSCEL |
|--|----------------------|----------------------|-------------------------|--------------------|
| <b>Age (mean-yrs)</b>                    | 60.3                 | 64.3                 | 64.6                    | 62                 |
| <b>Duration of Diabetes (median-yrs)</b> | 9.3                  | 12.8                 | 13.9                    | 12                 |
| <b>Baseline HgbA1c (mean)</b>            | 7.6                  | 8.7                  | 8.7                     | 8                  |
| <b>Established ASCVD- %</b>              | --                   | 81.4                 | 72.1                    | 73.1               |
| <b>Hypertension - %</b>                  | 76.4                 | --                   | 92.8                    | --                 |
| <b>Prior HF - %</b>                      | 22.4                 | 17.8                 | 23.6                    | 16.2               |
| <b>Current smoker</b>                    | 11.7                 | --                   | NR                      | 11.7               |
| <b>Qualifying ACS Event - %</b>          |                      | Not applicable       | Not applicable          | Not applicable     |
| NSTEMI                                   | 38.6                 |                      |                         |                    |
| STEMI                                    | 43.9                 |                      |                         |                    |
| Unstable angina                          | 17.2                 |                      |                         |                    |

NSTEMI= non-ST-elevation myocardial infarction;  
STEMI= ST-elevation myocardial infarction

Pfeiffer MA et al. *NEJM*. 2015;373(23):2247-57.  
Marso SP et al. *NEJM*. 2016;375(4):311-22.  
Marso SP et al. *NEJM*. 2016;375(19):1834-44.  
Holman RR et al. *NEJM*. 2017;377(13):1228-39.

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## GLP-1 Agonists: Results

|   | Lixisenatide / ELIXA                 |              | Liraglutide / LEADER                     |         | Semaglutide / SUSTAIN-6                  |                   | Exenatide / EXSCEL |                    |
|---|--------------------------------------|--------------|--|---------|--|-------------------|--------------------|--------------------|
|   | HR (95%CI)                           | P Value      | HR (95%CI)                               | P Value | HR (95%CI)                               | P Value           | HR (95%CI)         | P Value            |
| <b>Primary Composite</b>                              | 1.02 (0.89-1.17)                     | 0.81         | 0.87 (0.78-0.97)                         | 0.01    | 0.74 (0.58-0.95)                         | <0.001*<br>0.02^^ | 0.91 (0.83-1.00)   | <0.001*<br>0.061^^ |
| <b>Secondary Composite(s)</b>                         | 0.97 (0.85-1.10)<br>1.00 (0.90-1.11) | 0.63<br>0.96 | 0.88 (0.81-0.96)                         | 0.005   | 0.74 (0.62-0.89)                         | 0.002             | --                 | --                 |
| <b>Death from CV causes</b>                           | 0.98 (0.78-1.22)                     | 0.85         | 0.78 (0.66-0.93)                         | 0.007   | 0.98 (0.65-1.48)                         | 0.92              | 0.88 (0.76-1.02)   | 0.628              |
| <b>Nonfatal MI</b>                                    | 1.03 (0.87-1.22)                     | 0.71         | 0.88 (0.75-1.03)                         | 0.11    | 0.74 (0.51-1.08)                         | 0.12              | 0.95 (0.84-1.09)   | 0.628              |
| <b>Nonfatal stroke</b>                                | 1.12 (0.79-1.58)                     | 0.54         | 0.89 (0.72-1.11)                         | 0.30    | 0.61 (0.38-0.99)                         | 0.04              | 0.86 (0.70-1.07)   | 0.628              |
| <b>Death from any cause</b>                           | 0.94 (0.78-1.13)                     | 0.50         | 0.85 (0.74-0.97)                         | 0.02    | 1.05 (0.74-1.50)                         | 0.79              | 0.86 (0.77-0.97)   | --                 |
| <b>Hospitalization for UA</b>                         | --                                   | --           | 0.98 (0.76-1.26)                         | 0.87    | 0.82 (0.47-1.44)                         | 0.49              | --                 | --                 |
| <b>Hospitalization for HF</b>                         | 0.96 (0.75-1.23)                     | 0.75         | 0.87 (0.73-1.05)                         | 0.14    | 1.11 (0.77-1.61)                         | 0.57              | 0.94 (0.78-1.13)   | --                 |
| <b>Hospitalization for coronary revascularization</b> | --                                   | --           | 0.91 (0.80-1.04)                         | 0.18    | 0.65 (0.50-0.86)                         | 0.003             | --                 | --                 |
| <b>Other Study Notes</b>                              |                                      |              | ↓ progression of renal disease (p 0.003) |         | ↓ progression of renal disease (p 0.005) |                   |                    |                    |
| <b>FDA Approved Indication?</b>                       | NO                                   |              | YES                                      |         | NO                                       |                   | NO                 |                    |

Pfeiffer MA et al. *NEJM*. 2015;373(23):2247-57.  
Marso SP et al. *NEJM*. 2016;375(4):311-22.  
Holman RR et al. *NEJM*. 2017;377(13):1228-39.

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## Study Critique and Future Considerations

### Limitations

- Lack of generalizability
- Short timeline for assessing potential benefits and harm
- Placebo-controlled design

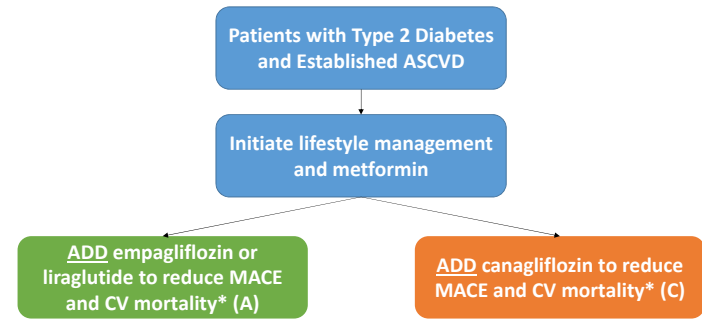
### Considerations for Future Trials

- More diverse, lower-risk populations
- Longer follow-up
- Active comparators
- Innovative designs
- Standardized definitions for safety of microvascular outcomes
- Modifications of end points and analyses
- Establishment of biorepositories
- Enhanced efficacy and cost-sharing options
- Involvement of patients and advocacy organizations

American Diabetes Association. Diabetes Care. 2018;41:14-31.

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## 2018 Standards of Care Recommendations



\*= Consider patient and drug-specific factors in decision making

American Diabetes Association. Diabetes Care. 2018;41(Suppl 1):S73-S85.

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## Patient Case: Question #2

SN's baseline hemoglobin A1c 6 months ago was 9.5%. He was initially started on metformin 500 mg PO BID, and titrated to 1000 mg PO BID approximately three months ago. He denies missing any doses. Today, his hemoglobin A1c is 7.8%. He would like to hold off on any injectable agents at this time if possible.

Taking into account his patient-specific factors, which of the following is best to initiate to achieve optimal glycemic control?

- Canagliflozin
- Empagliflozin
- Liraglutide
- Sitagliptin

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## Learning Objectives - Pharmacist

- Apply recent changes to blood pressure goals in patients with diabetes
- Assess the role of new antihyperglycemic therapies in preventing major adverse cardiovascular events
- **Discuss the benefits, concerns, and barriers when incorporating new cardiovascular risk strategies in patients with diabetes**

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## Barriers to Managing CV Risk

- Access
- Complexities in treatment
- Knowledge gaps
- Coordination of care
- Time

Survey looks at barriers, opportunities for managing CV risk in diabetes patients. *Cardiology*, August 2017: 23.

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## Access

- Cost
  - Large concern of both providers and patients
  - Many new medications are non-formulary or are typically on higher tiers for cost
    - Patients often have to decide if they pay their utility bill or their co-pay
  - Using coupon cards works for certain patients
- Prior authorizations
  - While some newer medications can be prescribed via prior authorizations, the process is time-intensive
  - The more difficult it is to get through, the less likely providers are to use it

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## Complexity of Treatment

- Patients have multiple co-morbidities and each disease state may require multiple treatments
- Difficult to implement lifestyle changes, e.g. diet modification, weight loss, and regular exercise
  - Conflicting information exists to patients regarding diet making it even more difficult to implement

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## Gaps in Knowledge

- Clinicians
  - Understanding of new data from recent clinical trials is a huge critical gap
    - If you don't know the data, then you don't practice it
    - Increasing provider understanding should increase "buy-in" on newer therapies
- Patients
  - Trained to use surrogate markers as a measure of how well they are doing
  - Example - LDL
    - Adding a statin medication to patients whose fasting lipid panel is within range presents challenges

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## Coordinated Care

- Coordinating care among providers (cardiology, endocrinology, primary care) presents challenges
- Physicians may be concerned about “stepping on toes”



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## Time

- It takes a good amount of time to spend with patients to discuss the pros/cons of newer therapies
- Many providers just are not given the opportunity to do so given the typical visit is 15-20 minutes to cover more than just diabetes care



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## Issues that may arise while discussing CV outcome with patients

- “My doctor said my cholesterol is fine. Why would I need a medication for cholesterol?”
- Adding a statin to patients whose fasting lipid panel is within range presents challenges
  - Explaining to patients the reasoning behind the addition
  - Helps that high-intensity statin therapy is available at a low cost



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## Patient Concerns with Medications

- “Aren’t there other medications that are cheaper to control my diabetes?”
- Adding a GLP-1 agonist or SGLT-2 inhibitor with good CV data presents challenges
  - Explaining to patients the reasoning behind the addition, the pros/cons of each medication to treat diabetes
  - Discussing long-term benefits of taking a medication with good CV data



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## Adherence

- “I feel fine. Why do I need take my medication if my glucose is within goal range.”
- Explaining the purpose of medications and why it’s important to maintain adherence even if glucose levels are within range



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## Patient Case: Review

SN

- 56-year-old male
- BP 148/86, P 78, RR 14, T 37.8 °C
- Glucose log reveals readings > 200 over the past couple of months
- Hemoglobin A1c: 9.5% (6 months ago); 7.8% (today)

| Past Medical History   | Current Medications   | Social History   | Family History  |
|--|---|--|---|
| Type 2 DM<br>Hypertension<br>Hyperlipidemia<br>Peripheral vascular disease | Lisinopril 5 mg PO daily<br>Metformin 1000 mg PO BID<br>Atorvastatin 20 mg PO daily | Former smoker<br>Denies alcohol<br>Denies illicit substances | Father: alive, history of heart disease<br>Mother: died from stroke complications |



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## Patient Case: Question #3

In the case of SN, what barriers or challenges may arise when optimizing his cardiovascular risk profile?



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Questions?



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