Everything Old is New Again: Inflammation, Colchicine, and CVD Risk

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Disclosure:

Dr. Mora has served as a consultant to Pfizer and Quest Diagnostics
Topics to be Discussed

1. The early history of inflammation

2. Distinction between “residual cholesterol risk” and “residual inflammatory risk” as these patient groups have different reasons for recurrent events.

3. Anti-inflammatory therapies for CVD prevention: The central role of the IL-1\(\beta\) to IL-6 pathway of innate immunity.
   - CANTOS, CIRT trials
   - LoDoCo, COLCOT, LoDoCo2 trials

4. Lifestyle therapy to lower inflammation and cardiovascular risk.
The Early History of Inflammation

inflammatory condition: “When you examine a man with an irregular wound . . . and that wound is inflamed . . . [there is] a concentration of heat; the lips of that wound are reddened and that man is hot in consequence . . . then you must make cooling substances for him to draw the heat out . . . leaves of the willow”. Other remedies

(Onion crushed with honey and taken with a beer)
The Early History of Inflammation

• Assyrians (Sumerian tablets): Anti-inflammatory effects of the willow tree leaves

• Egyptians (Ebers papyrus):

Inflammatory condition: “When you examine a man with an irregular wound . . . and that wound is inflamed . . . [there is] a concentration of heat; the lips of that wound are reddened and that man is hot in consequence . . . then you must make cooling substances for him to draw the heat out . . . leaves of the willow”. Other remedies

(Onion crushed with honey and taken with a beer)
Raw and Red-Hot

Could inflammation be the cause of myriad chronic diseases?

Jonathan Shaw, Harvard Magazine; 2019;46-52
Raw and Red-Hot

Could inflammation be the cause of myriad chronic diseases?
Cardiovascular Disease Is An Inflammatory Disease
JUPITER

Primary Trial Endpoint: MI, Stroke, UA/Revascularization, CV Death

HR 0.56, 95% CI 0.46-0.69
P < 0.00001

- 44 %

Ridker PM et al NEJM 2008;359:2195-2207
**2018/2019 ACC/AHA Risk Enhancing Factors**

- **Risk Enhancers**
  - **Family History**
    - premature ASCVD (men <55 y, women <65 y)
  - **Pregnancy/Menopause**
    - preeclampsia
    - premature menopause
  - **Ethnicity**
  - **Biomarkers**
    - eGFR 15-59
    - LDL-C ≥ 160 mg/dL
    - Non-HDL-C ≥ 190 mg/dL
    - TGs ≥ 175 mg/dL
    - ApoB ≥ 130 mg/dL
    - Lp(a) ≥ 50 mg/dL or ≥ 125 nmol/L
    - ABI <0.9
    - hs-CRP ≥ 2 mg/L
  - **Chronic Inflammation**
  - **Metabolic Syndrome**
  - **RA, lupus, psoriasis, HIV**

*Grundy et al JACC 2019;73: e285*
How Common is Residual Inflammatory Risk? 
As Common as Residual Cholesterol Risk

Ridker JACC 2018;72:3320-3331
Resolution of Inflammation is an Active Process

From CRP to IL-6 to IL-1
Moving *Upstream* to Identify Novel Targets for Atheroprotection

**NLRP3 Inflammasome Caspase-1**
- Pro-IL-18
- Pro-IL-1β
- Activated IL-18
- Activated IL-1β

**Microtubule Polymerization Inhibitors**
- Colchicine

**Interleukin-1 Inhibitors**
- Canakinumab (IL-1b mAB)
- Gevokizumab (IL-1b mAB)
- Rilonacept (IL-1 TRAP)
- Anakinra (IL-1Ra)

**Interleukin-6 Inhibitors**
- Tocilizumab
- Sarilumab
- Sirukimab
- Olokizumab
- Ziltikevimab

**Interleukin-18 Inhibitors**
- IL-18
- IL-1β

**C-reactive Protein**
- hsCRP
- > 3 mg/L
  - High Vascular Risk
- <1 mg/L
  - Low Vascular Risk

Ridker PM. Circulation 2020;141:787-789
Interleukin-1β Inhibition
Canakinumab 150 mg SQ/3 mo

- IL-1β
- IL-6
- hsCRP
- 15-17% reduction in MACE and MACE+
- 50-70% reduction in Lung Cancer

Low-Dose Methotrexate
15-20 mg po / wk

- IL-1β
- IL-6
- hsCRP
- No reduction in MACE and MACE+
- No reduction in Lung Cancer
- Non-basal cell Skin Cancer

Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease

Stefan M. Nidorf, MD, MBBS,* John W. Eikelboom, MD, MPH,††‡§ Peter L. Thompson, MD§

Perth, Australia; and Hamilton, Ontario, Canada

N = 532
Colchicine 0.5 mg po qd

Open label
No Placebo
Single Center

55 total events
15 colchicine, 40 control

All Cause Mortality
4 colchicine, 10 control

HR 0.33 (95% CI 0.18 – 0.59)
P<0.001

LoDoCo Trial

Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction

Jean-Claude Tardif, M.D., Simon Kouz, M.D., David D. Waters, M.D., Olivier F. Bertrand, M.D., Ph.D., Rafael Díaz, M.D., Aldo P. Maggioni, M.D., Fausto J. Pinto, M.D., Ph.D., Reda Ibrahim, M.D., Habib Gamra, M.D., Ghassan S. Kiwan, M.D., Colin Berry, M.D., Ph.D., José López-Sendón, M.D., Petr Ostadal, M.D., Ph.D., Wolfgang Koenig, M.D., Denis Angoulvant, M.D., Jean C. Grégoire, M.D., Marc-André Lavoie, M.D., Marie-Pierre Dubé, Ph.D., David Rhainds, Ph.D., Mylène Provancher, Ph.D., Lucie Blondeau, M.Sc., Andreas Orfanos, M.B., B.Ch., Philippe L. L'Allier, M.D., Marie-Claude Guertin, Ph.D., and François Roubille, M.D., Ph.D.

ABSTRACT

HR 0.77 (95% CI 0.61 – 0.96)
P=0.02

<table>
<thead>
<tr>
<th>Months since Randomization</th>
<th>Cumulative Incidence (%)</th>
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<tr>
<td></td>
<td>Placebo</td>
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<tr>
<td>0</td>
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<td>7</td>
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<td>35</td>
<td>90</td>
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<tr>
<td>42</td>
<td>100</td>
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No. at Risk

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<tr>
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<th>Placebo</th>
<th>Colchicine</th>
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<tbody>
<tr>
<td></td>
<td>2379</td>
<td>2366</td>
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<tr>
<td>7</td>
<td>2261</td>
<td>2284</td>
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<td>14</td>
<td>1854</td>
<td>1868</td>
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<td>21</td>
<td>1224</td>
<td>1230</td>
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<td>28</td>
<td>622</td>
<td>628</td>
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<td>35</td>
<td>144</td>
<td>153</td>
</tr>
<tr>
<td>42</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

Tardif JC., et al;
Study design

Post-myocardial infarction ≤30 days (n=4745 patients)
On statin, anti-platelet agents, ±RAASi, ±BB

Treated according to national guidelines
PCI completed if applicable

Colchicine 0.5 mg daily *
Placebo daily *

Primary composite endpoint: Time to first of CV death, cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring coronary revascularization

Secondary endpoints: Components of primary; composite of CV death, cardiac arrest, MI or stroke; total mortality

*provided by Pharmascience (Montreal)
## Secondary Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Colchicine (N = 2366)</th>
<th>Placebo (N = 2379)</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
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<tbody>
<tr>
<td><strong>Primary Composite</strong></td>
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<td></td>
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</tr>
<tr>
<td>MI, CVA, CV arrest, urgent revascularization, CVD</td>
<td>131</td>
<td>170</td>
<td>0.77</td>
<td>0.61-0.96</td>
<td>0.02</td>
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<tr>
<td><strong>Secondary Composite</strong></td>
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<td></td>
<td></td>
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<tr>
<td>MI, CVA, CV arrest, CVD</td>
<td>111</td>
<td>130</td>
<td>0.85</td>
<td>0.66-1.10</td>
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<tr>
<td>MI</td>
<td>89</td>
<td>98</td>
<td>0.91</td>
<td>0.68-1.21</td>
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<tr>
<td>CV Death</td>
<td>20</td>
<td>24</td>
<td>0.84</td>
<td>0.46-1.52</td>
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<tr>
<td>Resuscitated Cardiac Arrest</td>
<td>5</td>
<td>6</td>
<td>0.83</td>
<td>0.25-2.73</td>
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<tr>
<td>All Cause Mortality</td>
<td>43</td>
<td>44</td>
<td>0.98</td>
<td>0.64-1.49</td>
<td></td>
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<tr>
<td>Urgent Revascularization</td>
<td>25</td>
<td>50</td>
<td>0.50</td>
<td>0.31-0.81</td>
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<tr>
<td>Stroke</td>
<td>5</td>
<td>19</td>
<td>0.26</td>
<td>0.10-0.70</td>
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<tr>
<td>Pneumonia</td>
<td>21</td>
<td>9</td>
<td></td>
<td></td>
<td>0.03</td>
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</table>
ESC Colchicine II : LoDoCo-2 (Chronic CAD, N = 5522)

Colchicine in Patients with Chronic Coronary Disease


264 placebo vs 187 colchicine
HR 0.69 (95% CI 0.57 – 0.83)
P<0.001

No. at Risk
Placebo 2760 2655 1703 821 590 161
Colchicine 2762 2685 1761 890 629 166

ESC Colchicine II: LoDoCo-2 (Chronic CAD, N = 5522)

264 placebo vs 187 colchicine
HR 0.69 (95% CI 0.57 – 0.83)
P<0.001

LoDoCo2 Protocol

Patients aged 35 – 82 years with **proven coronary disease**
**Clinically stable ≥6 months**
No advanced renal disease, heart failure or severe valvular heart disease

30-day open label run-in of colchicine 0.5mg daily

Tolerant, clinically stable and willing

Colchicine  
Placebo

15.4% drop-out
Pre-randomization

Planned to begin close-out 12 months after the last participant had been randomized*

* If 331 primary events had accrued – sufficient to detect a 30% effect of therapy with 90% power

### Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Colchicine (N=2762)</th>
<th>Placebo (N=2760)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>65.8 ±8.4</td>
<td>65.9 ±8.7</td>
</tr>
<tr>
<td>Male</td>
<td>2305 (83.5)</td>
<td>2352 (85.9)</td>
</tr>
</tbody>
</table>

#### Risk Factors and History

- **Current Smoker**: 318 (11.5) | 330 (12.0)
- **Hypertension**: 1421 (51.4) | 1387 (50.3)
- **Diabetes**: 492 (17.8)     | 515 (18.7)
- **Prior Revascularization**: 2419 (83.4) | 2468 (84.0)
- **Prior ACS**: 2323 (84.1)    | 2335 (84.6)
- **Last ACS >24m**: 1570 (67.6) | 1609 (68.9)

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### LoDoCo-2 Secondary Endpoints

<table>
<thead>
<tr>
<th>Event</th>
<th>Colchicine (N = 2762)</th>
<th>Placebo (N = 2760)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cardiovascular death, Myocardial infarction, or Ischemic stroke</td>
<td>115 (4.2)</td>
<td>157 (5.7)</td>
<td>0.72 (0.57-0.92)</td>
<td>0.007</td>
</tr>
<tr>
<td>2. Myocardial infarction or Ischemia-driven coronary revascularization</td>
<td>155 (5.6)</td>
<td>224 (8.1)</td>
<td>0.67 (0.55-0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3. Cardiovascular death or Myocardial infarction</td>
<td>100 (3.6)</td>
<td>138 (5.0)</td>
<td>0.71 (0.55-0.92)</td>
<td>0.010</td>
</tr>
<tr>
<td>4. Ischemia-driven coronary revascularization</td>
<td>135 (4.9)</td>
<td>177 (6.4)</td>
<td>0.75 (0.60-0.94)</td>
<td>0.012</td>
</tr>
<tr>
<td>5. Myocardial infarction</td>
<td>83 (3.0)</td>
<td>116 (4.2)</td>
<td>0.70 (0.53-0.93)</td>
<td>0.014</td>
</tr>
<tr>
<td>6. Ischemic stroke</td>
<td>16 (0.6)</td>
<td>24 (0.9)</td>
<td>0.66 (0.35-1.25)</td>
<td></td>
</tr>
<tr>
<td>7. Cardiovascular death</td>
<td>20 (0.7)</td>
<td>25 (0.9)</td>
<td>0.80 (0.44-1.44)</td>
<td></td>
</tr>
</tbody>
</table>
Residual Inflammatory or Cholesterol Risk?

Residual Cholesterol Risk

- LDL 110 mg/dL
- hsCRP 1.8 mg/L

  Additional LDL Reduction

  IMPROVE-IT: Ezetimibe 6% RRR
  FOURIER/SPIRE/ODYSSEY: PCSK9 Inhibition q2 weeks 15-20% RRR

Residual Inflammatory Risk

- LDL 70 mg/dL
- hsCRP 3.8 mg/L

  Additional Inflammation Reduction

  LoDoCo Colchicine 0.5 mg po qd 67% RRR
  CANTOS Canakinumab 150mg SC q 3 mo 15-20%RRR
  COLCOT Colchicine 0.5mg po qd 24%RRR
  LoDoCo2 Colchicine 0.5 mg po qd 30% RRR

Modified from Ridker PM, Eur Heart J 2016;37:1720-22
Non-Pharmacologic Approaches to Inflammation Resolution

Mediterranean Diet

- Inflammation
- Diabetes Metabolism and Insulin Resistance
- Age
- HDL measures
- Obesity
- Genetics
- Hypertension
- VLDL measures
- Branched chain amino acids
- Smoking

CVD

Ahmad S et al.  
*JAMA Net Open* 2019
Mediterranean Diet Lowers Chronic Inflammation

% of CVD Benefit Explained by Various Risk Factors

- Inflammation: 29%
- Insulin Resistance/ Glucose Metabolism: 28%
- Body Mass Index: 27%
- Blood Pressure / Hypertension: 26.6%
- Traditional Lipids: 26%
- HDL Measures: 26.6%
- VLDL Measures: 25.5%
- LDL Measures: 24.4%
- Branched Chain Amino Acids: 23.3%
- Apolipoproteins: 22.2%
- Small Molecule Metabolites: 21.1%

Ahmad S et al.
JAMA Net Open 2018; 1:e185708
Physical Activity Lowers Chronic Inflammation

% of CVD Benefit Explained by Various Risk Factors

- All Risk Factors: 59%
- Inflammation: 32.6%
- Blood Pressure / Hypertension: 27.1%
- Traditional Lipids: 19.1%
- Novel Lipids: 15.5%
- Body Mass Index: 10.1%
- Hemoglobin A1c / Diabetes: 8.9%
- Homocysteine: 0.7%

Mora et al, Circulation 2007;116: 2110-8
Inflammation and Cardiovascular Disease 2021

Summary (1)

1. Atherosclerosis is a lipid-driven inflammatory disease.

2. In primary prevention, the JUPITER trial proved that adults with chronic inflammation benefit from statin therapy even if LDL cholesterol levels are low.

3. In secondary prevention, the CANTOS trial provided proof-of-principle that inflammation inhibition, in the absence of lipid lowering, can improve atherothrombotic outcomes. The positive CANTOS data and the neutral CIRT data for methotrexate define the central \textbf{IL-1\textbeta to IL-6 pathway} of innate immunity as crucial for CVD protection.
4. The COLCOT and LoDoCo2 trials provide clinically important independent confirmation of the inflammation hypothesis with an apparently safe and much less expensive oral agent, colchicine.

5. Distinction between “residual cholesterol risk” and “residual inflammatory risk” as these patient groups have different reasons for recurrent events.

6. The Mediterranean diet, exercise, and smoking cessation all lower inflammation and cardiovascular risk.
Inflammation and Cardiovascular Disease 2021

Take Home Message

It can be anticipated that cardiovascular patients will receive aggressive lipid lowering and inflammation inhibiting therapy (e.g. colchicine), in addition to behavioral and lifestyle interventions.
Topics Discussed

1. The early history of inflammation

2. Distinction between “residual cholesterol risk” and “residual inflammatory risk” as these patient groups have different reasons for recurrent events.

3. Anti-inflammatory therapies for CVD prevention: The central role of the IL-1β to IL-6 pathway of innate immunity.
   - CANTOS, CIRT trials
   - LoDoCo, COLCOT, LoDoCo2 trials

4. Lifestyle therapy to lower inflammation and cardiovascular risk.
It’s Much More than Just Glucose Lowering in Diabetes: Role of SGLT2i & GLP1-RAs in ASCVD Risk Reduction

Kittie Wyne, MD, PhD, FACE, FNLA
Professor of Clinical Medicine
Division of Endocrinology, Diabetes & Metabolism

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER
February 24, 2021
Conflict of Interest

- Research funding: Sanofi, Allergan
- Advisory Boards: Novo Nordisk, Esperion

None of these activities are related to GLP1s
Objectives

- Assess the implications of recent outcomes trials for the clinical management of patients with diabetes.

Circ, 2020:142:e265-e288; NEJM 2016; 375:1797-1799
Milestones in the Treatment of Diabetes in the US

How Did We Get Here?


Insulin
GLP-1 RAs
Metformin
UGDP
ACCORD
ADVANCE
VADT
SUs
DPP-4 inhibitors
BAR, Bromocriptine-QR
Analog Insulin, TZDs
DCCT
DPP
Inhaled Insulin
CGM
Inhaled degludec
FDCs: basal insulin + GLP1
Insulin glargine
degludec
SGLT-2 inhibitors
DCCT
Faster acting insulin aspart

© Wyne 2021
The US FDA 2008

- **July, 2008**: FDA asked the Endocrine & Metabolism Advisory Committee: “Should Glucose Lowering Agents Undergo CV Outcomes Trials Prior to FDA Approval?”

- **December 2008**: FDA Response
  - Drugs already filed with the FDA will review their current data and may be required to complete a CV outcomes trial
  - Drugs in development will need to show that they do not have a “signal”
  - They chose to use an upper 95% CI of 1.8
  - This will require at least 122 total CV events
    - Note: event rate in ACCORD was ~2%/year
Diabetes CV Outcomes Trials (CVOT): *completed*

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<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Enrollment</th>
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<tbody>
<tr>
<td>ORIGIN</td>
<td>Insulin glargine</td>
<td>12,537</td>
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<tr>
<td>SAVOR</td>
<td>DPP-4 Inhibitor: saxagliptin</td>
<td>16,492</td>
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<td>EXAMINE</td>
<td>DPP-4 Inhibitor: alogliptin</td>
<td>5,384</td>
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<td>TECOS</td>
<td>DPP-4 Inhibitor: sitagliptin</td>
<td>14,000</td>
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<tr>
<td>ELIXA</td>
<td>GLP-1 RA: lixisenatide</td>
<td>6,000</td>
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<tr>
<td>EXSCEL</td>
<td>GLP-1 RA: weekly exenatide</td>
<td>14,000</td>
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<tr>
<td>LEADER</td>
<td>GLP-1 RA: liraglutide</td>
<td>9,340</td>
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<td>DEVOTE</td>
<td>Insulin Degludec</td>
<td>7,500</td>
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<td>CANVAS</td>
<td>SGLT2 inhibitor: canagliflozin</td>
<td>10,143</td>
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<tr>
<td>SUSTAIN 6</td>
<td>GLP1-RA: semaglutide</td>
<td>3,297</td>
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<td>EMPA-REG OUTCOME</td>
<td>SGLT2 inhibitor: empagliflozin</td>
<td>7,064</td>
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<td>ACE</td>
<td>AGI: acarbose</td>
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<td>AleCardio</td>
<td>Dual PPAR: Aleglitazar</td>
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<td>TOSCA.IT</td>
<td>TZD or SU add on to metformin</td>
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<td>Aspirin/Omega-3 fish oil</td>
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<td>REWIND</td>
<td>GLP-1 RA: dulaglutide</td>
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<td>CAROLINA</td>
<td>DPP-4 Inhibitor: linagliptin</td>
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<td>VERTIS CV</td>
<td>SGLT-2 inhibitor: ertugliflozin</td>
<td>8,000</td>
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<tr>
<td>CARMELINA</td>
<td>SGLT-2 inhibitor: canagliflozin</td>
<td>7,003</td>
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<tr>
<td>PIONEER</td>
<td>Oral GLP-1 RA: semaglutide</td>
<td>8,000</td>
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<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td><strong>195,117</strong></td>
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### The Alphabet: SGLT2i

Heart Failure, CVD & CKD

- EMPA-REG OUTCOME
- CANVAS Program
- DECLARE-TIMI 58
- CVD REAL
- VERTIS-CV
- CREDENCE
- DAPA-HF
- EMPEROR
- CVOT
- CVOT
- CVOT
- CVOT (real life)
- CVOT
- Renal
- HF
- HF
EMPA-REG OUTCOME®

- Randomised, double-blind, placebo-controlled CV outcomes trial
  - SGLT2 inhibitor vs placebo
- **Objective**
  To examine the long-term effects of empagliflozin versus placebo, in addition to standard of care, on CV morbidity and mortality in patients with type 2 diabetes and high risk of CV events
EMPA-REG OUTCOME®
All-cause mortality

Kaplan-Meier estimate. HR, hazard ratio
**EMPA-REG OUTCOME®**

**CV Death**

![Cumulative incidence function. HR, hazard ratio](image)

**HR 0.62**

(95% CI 0.49, 0.77)

*p* < 0.0001

---

**No. of patients**

Empagliflozin: 4687 4651 4608 4556 4128 3079 2617 1722 414

Placebo: 2333 2303 2280 2243 2012 1503 1281 825 177

---

**Cumulative incidence function. HR, hazard ratio**
EMP A-REG OUTCOME®: Summary

- Empagliflozin was associated with a reduction in A1c without an increase in hypoglycaemia, reductions in weight and BP, and small increases in LDL cholesterol and HDL cholesterol
- Empagliflozin:
  - reduced risk for 3-point MACE by 14%
  - reduced hospitalisation for heart failure by 35%
  - reduced CV death by 38%
  - improved survival by reducing all-cause mortality by 32%

- Why was everyone with T2DM NOT on empagliflozin by the end of 2015??
## CVOTs with SGLT2i

<table>
<thead>
<tr>
<th>Drug</th>
<th>EMPA-REG OUTCOME¹</th>
<th>CANVAS Program²</th>
<th>DECLARE-TIMI 58³</th>
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</thead>
<tbody>
<tr>
<td>Doses analysed</td>
<td>10 mg, 25 mg (once daily)</td>
<td>100 mg, 300 mg (once daily)</td>
<td>10 mg (once daily)</td>
</tr>
<tr>
<td>Median follow-up time, years</td>
<td>3.1</td>
<td>2.4</td>
<td>4.2</td>
</tr>
<tr>
<td>Trial participants</td>
<td>7020</td>
<td>10142</td>
<td>17160</td>
</tr>
<tr>
<td>Age, mean</td>
<td>63.1</td>
<td>63.3</td>
<td>63.9</td>
</tr>
<tr>
<td>Women</td>
<td>2004 (28.5%)</td>
<td>3633 (35.8%)</td>
<td>6422 (37.4%)</td>
</tr>
<tr>
<td>Patients with established atherosclerotic cardiovascular disease</td>
<td>7020 (100%)</td>
<td>6656 (65.6%)</td>
<td>6974 (40.6%)</td>
</tr>
<tr>
<td>Patients with a history of heart failure</td>
<td>706 (10.1%)</td>
<td>1461 (14.4%)</td>
<td>1724 (10.0%)</td>
</tr>
<tr>
<td>Patients with eGFR &lt;60 mL/min per 1.73 m²</td>
<td>1819 (25.9%)</td>
<td>2039 (20.1%)</td>
<td>1265 (7.4%)</td>
</tr>
</tbody>
</table>

Data are n (%) unless otherwise specified. The CANVAS Program consisted of two trials, CANVAS and CANVAS-R, but are presented combined. eGFR = estimated glomerular filtration rate.
Meta-analysis of SGLT2i RCTs: MACE Endpoint* stratified by the presence of established ASCVD

<table>
<thead>
<tr>
<th>Patients with atherosclerotic cardiovascular disease</th>
<th>Events</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (n) Placebo (n)</td>
<td>Treatment</td>
<td>Placebo</td>
<td>Treatment</td>
<td>Placebo</td>
</tr>
<tr>
<td>EMPA-REG OUTCOME 4687 2333 772</td>
<td>37.4</td>
<td>43.9</td>
<td>29.4</td>
<td>0.86 (0.74-0.99)</td>
</tr>
<tr>
<td>CANVAS Program 3756 2900 796</td>
<td>34.1</td>
<td>41.3</td>
<td>32.4</td>
<td>0.82 (0.72-0.95)</td>
</tr>
<tr>
<td>DECLARE-TIMI 58 3474 3500 1020</td>
<td>36.8</td>
<td>41.0</td>
<td>38.2</td>
<td>0.90 (0.79-1.02)</td>
</tr>
</tbody>
</table>

Fixed effects model for atherosclerotic cardiovascular disease ($p=0.0002$)

<table>
<thead>
<tr>
<th>Patients with multiple risk factors</th>
<th>Events</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (n) Placebo (n)</td>
<td>Treatment</td>
<td>Placebo</td>
<td>Treatment</td>
<td>Placebo</td>
</tr>
<tr>
<td>CANVAS Program 2039 1447 215</td>
<td>15.8</td>
<td>15.5</td>
<td>25.9</td>
<td>0.98 (0.74-1.30)</td>
</tr>
<tr>
<td>DECLARE-TIMI 58 5108 5078 539</td>
<td>13.4</td>
<td>13.3</td>
<td>74.1</td>
<td>1.01 (0.86-1.20)</td>
</tr>
</tbody>
</table>

Fixed effects model for multiple risk factors ($p=0.98$)

*MAE (major adverse CV events) composite of MI, stroke, and CV death

Meta-analysis of SGLT2i RCTs: Summary

- Hospitalisation for heart failure:
  - 31% reduction in relative risk

- Progression of renal disease:
  - 45% reduction in relative risk

- MACE:
  - 11% reduction in relative risk
  - No benefit in the multiple risk factor group

Empagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus,
- to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease. (1)

Canagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1)
- to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease (1)
- to reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria (1).
What About Heart Failure?
Hospitalisation for Heart Failure

HR 0.65
(95% CI 0.50, 0.85)
$p=0.0017$

Cumulative incidence function. HR, hazard ratio
Hospitalization for Heart Failure (HHF)
consistent benefit for SGLT2i but not GLP1*

<table>
<thead>
<tr>
<th>Trials</th>
<th>Patients</th>
<th>Events</th>
<th>Treatment Events per 100 ptyrs</th>
<th>Placebo Events per 100 ptyrs</th>
<th>Weights</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GLP1-RA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELIXA</td>
<td>6068</td>
<td>249</td>
<td>1.8</td>
<td>1.9</td>
<td>19.7</td>
<td>0.96 [0.75, 1.23]</td>
</tr>
<tr>
<td>LEADER</td>
<td>9340</td>
<td>466</td>
<td>1.2</td>
<td>1.4</td>
<td>36.4</td>
<td>0.87 [0.73, 1.05]</td>
</tr>
<tr>
<td>SUSTAIN-6</td>
<td>3297</td>
<td>113</td>
<td>1.8</td>
<td>1.6</td>
<td>8.8</td>
<td>1.11 [0.77, 1.61]</td>
</tr>
<tr>
<td>EXSCEL</td>
<td>14752</td>
<td>450</td>
<td>0.9</td>
<td>1.0</td>
<td>35.0</td>
<td>0.94 [0.78, 1.13]</td>
</tr>
<tr>
<td><strong>SGLT2i</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>7020</td>
<td>221</td>
<td>0.9</td>
<td>1.4</td>
<td>24.0</td>
<td>0.65 [0.50, 0.85]</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>10142</td>
<td>243</td>
<td>0.6</td>
<td>0.9</td>
<td>25.6</td>
<td>0.67 [0.52, 0.87]</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>17160</td>
<td>498</td>
<td>0.6</td>
<td>0.8</td>
<td>50.4</td>
<td>0.73 [0.61, 0.88]</td>
</tr>
</tbody>
</table>

Fixed Effects for HHF (P-value=0.20)

0.93 [0.83, 1.04]

*similar benefit was found in CREDEENCE;
Zelniker et al. Circulation 2019:2022
Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

- DAPA-HF study was designed to prospectively evaluate the efficacy and safety of the SGLT2i dapagliflozin in patients with heart failure and reduced ejection fraction (HFrEF), regardless of the presence or absence of diabetes
  - 41.7% had prior diagnosis of diabetes
- Phase III, randomized, placebo-controlled, multicenter trial
EMPEROR-Reduced Trial

- double-blind trial that randomized 3730 patients with class II, III, or IV HF and an LVEF of < 40% to receive empagliflozin (10 mg once daily) or placebo, in addition to recommended therapy.
  - 49.8% did have a prior diagnosis of diabetes
  - 6.6% were African-American

- The primary outcome was a composite of CV death or hospitalization for worsening heart failure.
  - for empagliflozin vs. placebo, was 19.4% vs. 24.7% (hazard ratio [HR] 0.75, 95% confidence interval [CI] 0.65-0.86, p < 0.001)
    - CV death: 10% vs. 10.8% (HR 0.92, 95% CI 0.75-1.12)
    - HF hospitalization: 13.2% vs. 18.3% (HR 0.69, 95% CI 0.59-0.81)
Secondary outcomes:

- Death/HF hospitalization/emergent or urgent HF visit requiring intravenous treatment or diuretic intensification/deterioration of NYHA class: 32.7% vs. 43% (p < 0.0001)
- Intensification of diuretics: 15.9% vs. 22.2% (p < 0.0001)
- Emergent or urgent HF visit requiring intravenous treatment: 6.8% vs. 9.9% (p = 0.0004)
- Hospitalization for HF requiring cardiac care unit/intensive care unit care: 4.8% vs. 5.7% (p = 0.002)
Dapagliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor indicated in adults for:

**Type 2 Diabetes Mellitus:**
- as an adjunct to diet and exercise to improve glycemic control. (1.1)
- to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease or multiple cardiovascular risk factors. (1.1)

**Heart Failure:**
- to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure with reduced ejection fraction (NYHA class II-IV). (1.2)
We recommend SGLT2 inhibitors, such as empagliflozin, canagliflozin or dapagliflozin, be used for treatment of patients with T2DM and ASCVD to reduce the risk of HF hospitalization and death (Strong Recommendation, High-Quality Evidence).

We recommend SGLT2 inhibitors, such as dapagliflozin be used in patients with T2DM aged > 50 years with additional risk factors for ASCVD to reduce the risk of HHF (Strong Recommendation, High-Quality Evidence).

We recommend SGLT2 inhibitors, such as canagliflozin, be used in patients aged > 30 years with T2DM, and macroalbuminemic renal disease, to reduce the risk of HF hospitalization and progression of renal disease (Strong Recommendation, High-Quality Evidence).

We recommend SGLT2 inhibitors, such as dapagliflozin be used in patients with mild to moderate HF due to reduced LVEF (≤ 40%) and concomitant T2DM, to improve symptoms and quality of life and to reduce the risk of hospitalization and CV mortality (Strong Recommendation, High-Quality Evidence).

We recommend SGLT2 inhibitors, such as dapagliflozin be used in patients with mild to moderate HF due to reduced LVEF (≤ 40%) and without concomitant diabetes, to improve symptoms and quality of life and to reduce the risk of hospitalization and cardiovascular mortality (Conditional Recommendation, High-Quality Evidence).

https://doi.org/10.1016/j.cjca.2019.11.036
The following are key points to remember from the 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment:

- For patients with newly diagnosed Stage C heart failure with reduced ejection fraction (HFrEF), a beta-blocker and an angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB)/angiotensin receptor-neprilysin inhibitor (ARNI) should be started in any order. Each agent should be up-titrated to maximally tolerated or target dose. Initiation of a beta-blocker is better tolerated when patients are dry and an ACEI/ARB/ARNI when patients are wet.

- Only guideline-recommended beta-blockers (i.e., carvedilol, metoprolol succinate, or bisoprolol) should be used in patients with HFrEF. Among angiotensin antagonists, ARNIs are preferred agents. Renal function and potassium should be checked within 1-2 weeks of initiation or dose up-titration of ACEI/ARB/ARNI.

- Diuretics should be added as needed and dose should be titrated to achieve decongestion. If doses in excess of furosemide 80 mg twice daily are needed, either a different loop diuretic should be considered or a thiazide should be added.

- After initiation of beta-blocker and angiotensin antagonist, addition of an aldosterone antagonist should be considered with close monitoring of electrolytes. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors should also be considered for HFrEF with New York Heart Association (NYHA) class II-IV patients.

SGLT2i: Questions to Explore

- Is there a CV benefit in Metabolic Syndrome?
- What about CKD4 & CKD5 in T2DM?
- Is there a renal benefit in the absence of T2DM?
- What about acute HF? or midrange LVEF?
- What about HFpEF?
  - Many patients with T2DM already have “diastolic dysfunction” at diagnosis
The Alphabet: GLP-1

CVD Events & Death

- LEADER
- EXSCEL
- REWIND
- HARMONY
- SUSTAIN 6
- PIONEER 6
The primary composite outcome was first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke.
# Cardiorenal Outcomes with GLP1s

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>ELIXA</th>
<th>LEADER</th>
<th>SUSTAIN-6</th>
<th>EXSCEL</th>
<th>REWIND</th>
<th>HARMONY</th>
<th>PIONEER-6</th>
<th>AWARD-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death, nonfatal MI, or nonfatal stroke, HR (95% CI)</td>
<td>1.02 (0.89–1.17)</td>
<td>0.87 (0.78–0.97)</td>
<td>0.74 (0.58–0.95)</td>
<td>0.91 (0.83–1.00)</td>
<td>0.88 (0.79–0.99)</td>
<td>0.78 (0.68–0.90)</td>
<td>0.79 (0.57–1.11)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death, HR (95% CI)</td>
<td>0.98 (0.78–1.22)</td>
<td>0.78 (0.66–0.93)</td>
<td>0.98 (0.65–1.48)</td>
<td>0.88 (0.76–1.02)</td>
<td>0.91 (0.78–1.06)</td>
<td>0.93 (0.73–1.19)</td>
<td>0.49 (0.27–0.92)</td>
<td></td>
</tr>
<tr>
<td>Fatal or nonfatal MI, HR (95% CI)</td>
<td>1.03 (0.87–1.22)</td>
<td>0.86 (0.73–1.00)</td>
<td>0.81 (0.57–1.16)</td>
<td>0.97 (0.85–1.10)</td>
<td>0.96 (0.79–1.15)</td>
<td>0.75 (0.61–0.90)</td>
<td>1.04 (0.66–1.66)</td>
<td></td>
</tr>
<tr>
<td>Fatal or nonfatal stroke, HR (95% CI)</td>
<td>1.12 (0.79–1.58)</td>
<td>0.86 (0.71–1.06)</td>
<td>0.65 (0.41–1.03)</td>
<td>0.85 (0.70–1.03)</td>
<td>0.76 (0.62–0.94)</td>
<td>0.86 (0.66–1.14)</td>
<td>0.76 (0.37–1.56)</td>
<td></td>
</tr>
<tr>
<td>Hospitalization for HF, HR (95% CI)</td>
<td>0.96 (0.75–1.23)</td>
<td>0.87 (0.73–1.05)</td>
<td>1.11 (0.77–1.61)</td>
<td>0.94 (0.78–1.13)</td>
<td>0.93 (0.77–1.12)</td>
<td>0.71 (0.53–0.94)</td>
<td>0.86 (0.48–1.55)</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality, HR (95% CI)</td>
<td>0.94 (0.78–1.13)</td>
<td>0.85 (0.74–0.97)</td>
<td>1.05 (0.74–1.50)</td>
<td>0.86 (0.77–0.97)</td>
<td>0.90 (0.80–1.01)</td>
<td>0.95 (0.79–1.16)</td>
<td>0.51 (0.31–0.84)</td>
<td></td>
</tr>
<tr>
<td>Worsening kidney function, HR (95% CI)</td>
<td>1.16 (0.74–1.83)</td>
<td>0.89 (0.67–1.19)</td>
<td>1.28 (0.64–2.58)</td>
<td>0.88 (0.74–1.05)</td>
<td>0.70 (0.57–0.85)</td>
<td></td>
<td></td>
<td>0.45 (0.20–0.97); dose of 1.5 mg</td>
</tr>
<tr>
<td>Definition of worsening kidney function</td>
<td>Doubling of serum creatinine or ≥40% decline in eGFR</td>
<td>Doubling of serum creatinine or ≥40% decline in eGFR</td>
<td>Doubling of serum creatinine or ≥40% decline in eGFR</td>
<td>Doubling of serum creatinine or ≥40% decline in eGFR, ESKD, death caused by kidney disease</td>
<td>Doubling of serum creatinine or ≥40% decline in eGFR</td>
<td></td>
<td></td>
<td>40% eGFR decline or ESKD outcomes</td>
</tr>
</tbody>
</table>

*Circ, 2020:142:e265-e288*
GLP1 Ras: CV summary

- Clear CV benefit in established CVD in short trials (2-3 years)
- REWIND was longer and showed a benefit in the multiple risk factor group (5.4 years)
  - Exploratory analysis suggested decrease in new albuminuria but not decline in eGFR or ESKD
LEADER

- FDA Aug 2017:

  Injectable semaglutide (SUSTAIN 6) now has the same indication:
  - as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1).
  - to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease (1).

- Injectabe semaglutide (SUSTAIN 6) now has the same indication

- Dulaglutide (REWIND Study)
  - to reduce the risk of major adverse CV events in adults with T2DM who have established CVD or multiple CV risk factors.

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated:
- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1).
- to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease (1).

Package insert: Victoza, Ozempic, Trulicity, accessed 2/1/2021
GLP1 Ras: Questions to Consider

- How early should you start them?
- What about pre-diabetes?
- What about Metabolic Syndrome?

**CV events begin at aprox 10 years after diagnosis of T2DM**
  - REWIND duration of follow-up was 5.4 years
    - This suggests that GLP-1 should be started within 5 years
  - ADA now rec GLP-1 before basal (unless symptomatic with very high A1c)
Summary

- **CVD:** SGLT2i & GLP-1 decrease CV events
- **Renal:** SGLT-2 decrease renal events
- **HF:** SGLT-2 decrease HF events

- How early do you want to start preventing CVD?
- How early do you want to start preventing HF?
  - Hint: diastolic dysfunction is HFP EF and is found early in T2DM
- How early do you want to start preventing CKD?
What About Guidelines?

- ADA/EASD
- AACE
- AHA
- ACC
- HFSA
- ESC
- CCS
Use Principles in Figure 9.1, including reinforcement of behavioral interventions (weight management and physical activity) and provision of DSMES to meet individualized treatment goals.

If injectable therapy is needed to reduce A1C\(^1\)

Consider GLP-1 RA in most patients prior to insulin\(^2\)

**INITIATION:** Initiate appropriate starting dose for agent selected (varies within class)

**TITRATION:** Titration to maintenance dose (varies within class)

If above A1C target

Add basal insulin\(^3\)

Choice of basal insulin should be based on patient-specific considerations, including cost. Refer to Table 9.3 for insulin cost information.

If already on GLP-1 RA or if GLP-1 RA not appropriate OR insulin preferred
To date, several large, well-conducted, randomized clinical trials have demonstrated that two novel classes of therapies originally developed for glucose lowering can directly improve CV outcomes.

The two classes of therapies are **SGLT2** (sodium-glucose cotransporter 2) **Inhibitors** and **GLP-1RAs** (glucagon-like peptide 1 receptor agonists). The specific drugs in each class that have demonstrated a reduction in major adverse CV events are:

<table>
<thead>
<tr>
<th>SGLT2 Inhibitors</th>
<th>canagliflozin, dapagliflozin, empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1RAs</td>
<td>dulanlutide, liaglutide, injectable semaglutide</td>
</tr>
</tbody>
</table>

Because most morbidity and mortality in T2D comes from CV events, the CV specialist has a key role in optimizing these patients’ care and is well-positioned to address 3 key areas in the management of patients with T2D: 1) Screening for T2D in their patients with or at high risk of CV disease; 2) Aggressively treating CV risk factors; and 3) Incorporating newer glucose-lowering agents with evidence for improving CV outcomes into routine practice.

CV specialists who care for patients with T2D, who also have one or more of the following: atherosclerotic cardiovascular disease (ASCVD)*, heart failure (HF), diabetic kidney disease (DKD)+, at high risk for ASCVD++, should recommend guideline-based therapy for prevention (lifestyle, blood pressure, lipids, glucose, antiplatelet), and initiate a patient-clinician discussion about the addition of an SGLT2 inhibitor or GLP-1RA with demonstrated CV benefit.
2020 ACC Expert Consensus Decision Pathway on Novel Therapies for CV Risk Reduction in Patients with T2DM

- Because most morbidity and mortality in T2DM comes from CV events, the CV specialist has a key role in optimizing these patients’ care and is well-positioned to address 3 key areas in the management of patients with T2DM:
  1) Screening for T2DM in their patients with or at high risk of CVD
  2) Aggressively treating CV risk factors
  3) Incorporating newer glucose-lowering agents with evidence for improving CV outcomes into routine practice

- CV specialists who care for patients with T2DM, who also have one or more of the following: ASCVD, HF, diabetic kidney disease (DKD), at high risk for ASCVD, should recommend guideline-based therapy for prevention (lifestyle, blood pressure, lipids, glucose, antiplatelet), and initiate a patient-clinician discussion about the addition of an SGLT2 inhibitor or GLP-1RA with demonstrated CV benefit.
Questions?

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Influenza Vaccination and Cardiovascular Disease Risk

Kevin C. Maki, PhD, CLS, FNLA
Indiana University, Department of Applied Health Science, School of Public Health, Bloomington, IN & Midwest Biomedical Research, Addison, IL
## Disclosures

<table>
<thead>
<tr>
<th>Pharmaceutical Company</th>
<th>Type of Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>89Bio</td>
<td>Consulting</td>
</tr>
<tr>
<td>Eli Lilly and Company</td>
<td>Consulting</td>
</tr>
<tr>
<td>Pepsico</td>
<td>Consulting</td>
</tr>
<tr>
<td>Acasti Pharma</td>
<td>Consulting, Research Grant</td>
</tr>
<tr>
<td>General Mills</td>
<td>Consulting, Research Grant</td>
</tr>
<tr>
<td>Kellogg’s</td>
<td>Consulting, Research Grant</td>
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<tr>
<td>Matinas BioPharma</td>
<td>Consulting, Research Grant</td>
</tr>
<tr>
<td>Novo Nordisk</td>
<td>Consulting, Research Grant</td>
</tr>
<tr>
<td>Pharmavite</td>
<td>Consulting, Research Grant</td>
</tr>
</tbody>
</table>
Estimated Influenza Disease Burden, by Season United States, 2010-11 through 2019-20 Influenza Seasons

Estimated U.S. Influenza Burden, By Season (2010 - 2020)

*Estimates for these seasons are preliminary and may change as data are finalized.

https://www.cdc.gov/flu/about/burden/index.html
During the 2019-2020 flu season, CDC estimates flu caused:

- **38 million** flu illnesses
  - About the same as the population of California

- **400,000** flu hospitalizations
  - About the same as the population of Miami, FL

- **22,000** flu deaths
  - Enough people to fill Madison Square Garden in New York City

Protective Efficacy of Influenza Vaccination

Estimated from CDC – US Vaccine Effectiveness Network
Effectiveness in preventing outpatient medical visits due to laboratory-confirmed influenza

Efficacy is dramatically low in case of mismatch between vaccine and circulating virus strains

the benefits of flu vaccination 2019-2020

Nearly 52% of the U.S. population aged 6 months and older got a flu vaccine during the 2019-2020 flu season, and this prevented an estimated:

- **7.5 million** flu illnesses
- **105,000** flu hospitalizations
- **6,300** flu deaths

- More than the combined population of Kentucky and Kansas
- Enough people to fill Michigan Stadium at the University of Michigan
- Equivalent to saving about 17 lives per day over the course of a year

“Domino” Effect of Influenza Exacerbates Chronic Health Conditions

Potential Mechanisms by Which Influenza May Increase Risk of Acute CV Complications

Lower Incidence of All-cause Death in the Elderly with History of MI Vaccinated for Influenza

- Patients ≥65 y of age who had been hospitalized for 1st episodes of myocardial infarction (MI)
- Vaccinated group received 1 dose of influenza vaccine within 180 d of discharge
- Propensity score-matched for known CVD risk factors

Hazard Ratio (95% CI) = 0.82 (0.72-0.92)

Lower Incidence of Recurrent MI + CV Death and of Hospitalization for Heart Failure in the Elderly with History of MI Vaccinated for Influenza

Hazard Ratio (95% CI) = 0.84 (0.74-0.96)

Hazard Ratio (95% CI) = 0.83 (0.74-0.92)

# Association of Influenza Vaccination and Risk of Recurrent MI or CV Death Across Subgroups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds Ratio (95% CI)</th>
<th>P-interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No/Other*</td>
</tr>
<tr>
<td>Sex, Male</td>
<td>0.86 (0.73-1.02)</td>
<td>0.81 (0.65-1.01)</td>
</tr>
<tr>
<td>Age, 65-75 y</td>
<td>0.93 (0.74-1.20)</td>
<td>0.80 (0.68-0.94)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.85 (0.74-0.97)</td>
<td>0.73 (0.40-1.31)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.81 (0.69-0.96)</td>
<td>0.89 (0.72-1.10)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>0.88 (0.73-1.07)</td>
<td>0.81 (0.67-0.98)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0.84 (0.70-1.01)</td>
<td>0.85 (0.70-1.03)</td>
</tr>
<tr>
<td>Statin use</td>
<td>0.79 (0.59-1.06)</td>
<td>0.86 (0.74-0.99)</td>
</tr>
<tr>
<td><strong>History of influenza vaccination</strong></td>
<td><strong>0.82 (0.70-0.96)</strong></td>
<td><strong>0.79 (0.61-1.02)</strong></td>
</tr>
</tbody>
</table>

*Other refers to female for sex and ≥75 y for age

Associations with all-cause death and hospitalization for heart failure were also consistent across subgroups

Lower Incidence of All-cause and CV Mortality in Patients with Diabetes Vaccinated for Influenza

241,551 patients in Denmark with diabetes and no heart disease, mean age 58.7 y
Monitored during 9 consecutive influenza seasons (Dec 1st through April 1st, 2007-2016)

<table>
<thead>
<tr>
<th></th>
<th>Events/PY</th>
<th>HR [95% CI]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not vaccinated</td>
<td>4,412/282,699</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Vaccinated</td>
<td>3,795/142,619</td>
<td>0.83 [0.78-0.88]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Cardiovascular death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not vaccinated</td>
<td>2,111/282,699</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Vaccinated</td>
<td>2,016/142,619</td>
<td>0.84 [0.77-0.91]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Stroke or AMI death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not vaccinated</td>
<td>727/282,699</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Vaccinated</td>
<td>712/142,619</td>
<td>0.85 [0.74-0.98]</td>
<td>0.028</td>
</tr>
</tbody>
</table>

Association Between Influenza Vaccination and All-cause Mortality by 2-month Periods Among Patients with Diabetes

<table>
<thead>
<tr>
<th>Months</th>
<th>HR [95% CI]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dec-Jan</td>
<td>0.79 [0.72-0.86]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Feb-Mar</td>
<td>0.87 [0.81-0.95]</td>
<td>0.001</td>
</tr>
<tr>
<td>Apr-May</td>
<td>0.85 [0.78-0.92]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Jun-Jul</td>
<td>0.91 [0.83-0.99]</td>
<td>0.021</td>
</tr>
<tr>
<td>Aug-Sept</td>
<td>0.89 [0.82-0.97]</td>
<td>0.007</td>
</tr>
<tr>
<td>Oct-Nov</td>
<td>0.91 [0.85-0.99]</td>
<td>0.024</td>
</tr>
</tbody>
</table>

Referent = no vaccination in the given season

Evidence Supporting Influenza Vaccination for Reducing Cardiovascular Risk

- Evidence is strong and consistent from observational studies
  - Potential for bias and confounding
- WHO recommends influenza vaccination for those with chronic medical conditions making placebo-controlled clinical trials difficult
  - But can enroll participants who are not otherwise planning to get vaccinated
- Two ongoing placebo-controlled trials
  - Influenza Vaccination Against Myocardial Infarction (IAMI): standard-dose trivalent and quadrivalent inactivated influenza vaccines vs. placebo in patients with ST-segment elevation MI (STEMI) or non-STEMI undergoing coronary angiography
  - Influenza Vaccine to Prevent Adverse Vascular Events (IVVE): standard-dose trivalent inactivated influenza vaccine vs. placebo in patients with heart failure

Adults ≥65 y of Age: An Important High-risk Group

Immune moderators in older persons
- Immune senescence
- Past exposures: vaccine/infection
- Frailty
- Biological age (≠ chronological age)
- Co-morbidity
- Medication

Potential vaccine solutions
- High-dose antigen
- Use of immune stimulants (adjuvants)
- Novel administration routes (intradermal)
- Multiple doses

High-dose Trivalent vs. Standard-dose Quadrivalent Influenza Vaccination

5,260 high-risk patients with recent MI or heart failure hospitalization with at least 1 additional risk factor, mean age 65.5 y

HR (95% CI) = 1.06 (0.97-1.17), p = 0.21

- Enrolled Sept. 21, 2016 to Jan. 31, 2019
- Last follow-up July 31, 2019
- Results consistent across subgroups
## Exploratory Analysis of SARS-CoV-2 Rates According to Non-COVID-19 Vaccination History

N = 137,037 propensity-score matched individuals who received SARS-CoV-2 PCR tests. Results shown are for vaccination within 1 y prior; results were similar for 2, 3 and 5 y.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Vaccinated COVID+ (%)</th>
<th>Unvaccinated COVID+ (%)</th>
<th>Relative Risk (95% CI)</th>
<th>BH-adjusted P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polio</td>
<td>2.66</td>
<td>4.70</td>
<td>0.57 (0.42- 0.77)</td>
<td>3.1E-03</td>
</tr>
<tr>
<td>MMR</td>
<td>3.12</td>
<td>5.53</td>
<td>0.56 (0.41-0.79)</td>
<td>3.2E-03</td>
</tr>
<tr>
<td>Geriatric flu</td>
<td>1.57</td>
<td>2.13</td>
<td>0.74 (0.61-0.89)</td>
<td>5.6E-03</td>
</tr>
<tr>
<td>Any flu</td>
<td>3.46</td>
<td>4.07</td>
<td>0.85 (0.75-0.96)</td>
<td>0.03</td>
</tr>
<tr>
<td>PCV13</td>
<td>2.17</td>
<td>3.03</td>
<td>0.72 (0.56-0.92)</td>
<td>0.03</td>
</tr>
<tr>
<td>Varicella</td>
<td>2.75</td>
<td>4.45</td>
<td>0.62 (0.42-0.92)</td>
<td>0.04</td>
</tr>
<tr>
<td>HepA-HepB</td>
<td>3.23</td>
<td>4.01</td>
<td>0.80 (0.67-0.97)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

BH=Benjamini-Hochberg-adjusted Fisher Exact test; Hep=hepatitis; MMR=measles-mumps-rubella; PCV13=pneumococcal conjugate

National Foundation for Infectious Diseases

• Issued a Call to Action titled: *The Dangers of Influenza and COVID-19 in Adults with Chronic Health Conditions*

• Downloadable resources for healthcare practitioners and patients to raise awareness about the importance of influenza prevention in patients with chronic health conditions is available at: [https://www.nfid.org/toolkits/flu-and-chronic-health-conditions/](https://www.nfid.org/toolkits/flu-and-chronic-health-conditions/)
Summary

• Influenza represents a substantial public health burden
• Influenza vaccination is typically 40-60% effective and prevents millions of illnesses and thousands of deaths each year
• Influenza exacerbates numerous chronic health conditions including cardiovascular disease; can trigger CV events
• Observational evidence: influenza vaccination associated with lower mortality, CV events and CV mortality among high-risk groups (elderly, history of CV disease, heart failure, and diabetes mellitus)
  – Consistent across subgroups and after adjustment for other factors
  – Most benefit in months with most influenza (December and January)
  – Bias and confounding? Those vaccinated are typically “healthier” overall but that seems unlikely to fully explain the associations observed.
Summary

• RCTs needed to evaluate causal relationship
  – High-dose vs. standard dose influenza vaccination in high-risk patients failed to demonstrate greater benefit
  – Two placebo-controlled RCTs ongoing
• Non-SARS-CoV-2 vaccinations, such as influenza vaccinations, may reduce the risk of getting COVID-19 (priming of the innate and adaptive immune responses)

Take home message:

Influenza vaccination is strongly recommended for individuals with chronic health conditions, particularly those with cardiovascular disease or risk factors such as diabetes mellitus.