Cochrane for Clinicians

Putting Evidence into Practice

DPP-4 Inhibitors, GLP-1 Receptor Agonists, and SGLT-2 Inhibitors for People With Cardiovascular Disease

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Clinical Question

Are dipeptidyl-peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and sodium-glucose cotransporter-2 (SGLT-2) inhibitors safe and effective at reducing cardiovascular mortality, all-cause mortality, and other cardiovascular outcomes (e.g., myocardial infarction, stroke, hospitalization from heart failure) in people with cardiovascular disease (CVD)?

Evidence-Based Answer

DPP-4 inhibitors do not reduce mortality or cardiovascular outcomes in people with CVD, and they increase the risk of pancreatitis. (Strength of Recommendation [SOR]: A, consistent, good-quality patient-oriented evidence.)

GLP-1 receptor agonists reduce cardiovascular mortality, all-cause mortality, and stroke in people with CVD. (SOR: A, consistent, good-quality patient-oriented evidence.)

SGLT-2 inhibitors reduce cardiovascular mortality, all-cause mortality, and hospitalization from heart failure in people with CVD.[1] (SOR: A, consistent, good-quality patient-oriented evidence.)

Practice Pointers

In the United States, CVD is the top cause of death, responsible for 24% of all deaths in 2019.[2] Diabetes mellitus is a leading cause of CVD.[3] Although metformin remains the first-line therapy for diabetes, with demonstrated cardiovascular benefit in people with or without diabetes, three newer medication classes were approved recently for diabetes management.[4] The authors of this review sought to determine if DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors improve outcomes in people with CVD regardless of whether they have diabetes.

This Cochrane review included 20 studies and 129,465 participants in several separate meta-analyses.[1] Participants 18 years and older who had baseline CVD with or without diabetes were recruited from across the world. This review included only placebo-controlled trials, and patients could be taking other medications to treat diabetes, including metformin, sulfonylureas, thiazolidinediones, and insulin. Treatment lasted 24 weeks or longer. Primary outcomes were cardiovascular mortality, myocardial infarction, and stroke. Secondary outcomes were all-cause mortality, hospitalization from heart failure, and adverse effects (including worsening renal function, hypoglycemia, pancreatitis, and fractures).

DPP-4 inhibitors (10 trials) did not improve any primary or secondary outcomes compared with placebo over three years.

GLP-1 receptor agonists were studied up to 3.8 years and reduced cardiovascular mortality (six trials; n = 46,093; number needed to treat [NNT] = 181; 95% CI, 109 to 531), all-cause mortality (seven trials; n = 46,393; NNT = 129; 95% CI, 82 to 307), and fatal and nonfatal stroke (five trials; n = 42,910; NNT = 268; 95% CI, 147 to 1,565), but they did not reduce myocardial infarctions or hospitalizations from heart failure, compared with placebo.

SGLT-2 inhibitors (five trials; n = 24,962) were studied for up to 3.5 years and reduced cardiovascular mortality (NNT = 48; 95% CI, 36 to 71), all-cause mortality (NNT = 43; 95% CI, 32 to 64), and hospitalization from heart failure (NNT = 19; 95% CI, 16 to 22), but they did not reduce myocardial infarctions or stroke, compared with placebo.

Regarding adverse effects, DPP-4 inhibitors increased the risk of pancreatitis (five trials; n = 47,684; number needed to harm = 860; 95% CI, 489 to 3,584) compared with placebo. GLP-1 receptor agonists (one trial; n = 3,297; NNT = 43; 95% CI, 26 to 121) and SGLT-2 inhibitors (two trials; n = 8,474; NNT = 109; 95% CI, 67 to 286) provided renal protection vs. placebo. Neither GLP-1 receptor agonists nor SGLT-2 inhibitors increased the risk of pancreatitis compared with placebo.

Limitations of this review include limited follow-up duration (metformin and its diabetes and cardiovascular outcomes have been under investigation since the 1950s) and the fact that some trials involved populations in which metformin was not used as a first-line therapy. Although all participants had baseline CVD, only three of the 20 pooled studies included people with CVD and without diabetes.

These are summaries of reviews from the Cochrane Library.

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A collection of Cochrane for Clinicians published in *AFP* is available at https://www.aafp.org/afp/cochrane.

CME This clinical content conforms to AAFP criteria for CME. See CME Quiz on page 18.

It was unclear if the benefits of these medications resulted from their effect on improving glucose control or occurred through an independent mechanism.

Despite a lack of head-to-head trials investigating these medications, the authors performed a network meta-analysis, a methodology that allows for comparisons of different interventions, provided the interventions have a common comparator (in this case, the medications were compared with placebo). The network meta-analysis in this review largely indicated that SGLT-2 inhibitors were likely best for reducing CVD and all-cause mortality.

The American Diabetes Association and the European Association for the Study of Diabetes recommend GLP-1 receptor agonists for people with diabetes and CVD. They also recommend SGLT-2 inhibitors for people with diabetes and heart failure, regardless of their atherosclerotic CVD risk score.[5] The American College of Cardiology recommends initiating a patient-physician discussion about SGLT-2 inhibitors and GLP-1 receptor agonists for people with diabetes and CVD (atherosclerotic CVD or heart failure).[6] Although there is robust evidence for the use of these medications in people with diabetes, the evidence is insufficient to support the use of these new medication classes (i.e., DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors) to improve cardiovascular outcomes in people without diabetes who have CVD.

Editor's Note: The NNTs and number needed to harm and their corresponding CIs reported in this Cochrane for Clinicians were calculated by the authors based on raw data provided in the original Cochrane review.

The practice recommendations in this activity are available at https://www.cochrane.org/CD013650.

The opinions and assertions expressed herein are those of the authors and do not reflect the official policy or position of the Uniformed Services University of the Health Sciences, the U.S. Army, or the Department of Defense.

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Palliative Care Interventions in Advanced Dementia

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Clinical Question

Are palliative care interventions effective in advanced dementia?

Evidence-Based Answer

Advance care planning interventions for people with advanced dementia likely increase the documentation of advance directives (relative risk [RR] = 1.23; 95% CI, 1.07 to 1.41) and the number of discussions about goals of care with family decision-makers (RR = 1.33; 95% CI, 1.11 to 1.59). These may slightly increase concordance with goals of care (RR = 1.39; 95% CI, 1.08 to 1.79). However, there is no effect on perceived symptom management as rated by family and nursing staff.[1] (Strength of Recommendation: C, limited-quality, disease-oriented evidence.)

Practice Pointers

Dementia is a debilitating, prevalent, and costly condition affecting more than 55 million people worldwide.[2,3] Despite dementia being a leading cause of death in the United States, palliative care interventions have not been widely utilized in the care of people affected by advanced dementia. Palliative care is an inclusive approach that focuses on the patient's quality of life as well as the caregivers who face problems associated with life-threatening illness.[4] The objective of this review is to assess the effectiveness of palliative care interventions in advanced dementia and to update a previous Cochrane review from 2016.[5]

This Cochrane review included nine studies (published between 2000 and 2020) involving 2,122 participants from the United States, Canada, the United Kingdom, and Europe.[1] Of the studies that met inclusion criteria, six were cluster randomized controlled trials (RCTs), two were individually randomized RCTs, and one was a controlled before-and-after study. The authors looked for studies evaluating the impact of palliative care interventions in adults with advanced dementia of any type. Participants were adults with advanced dementia, clinicians, family members, or other paid care staff. Studies were not excluded based on outcomes measured. Findings of palliative care

interventions were compared with usual care and reported advance care planning interventions and changes to the organization and delivery of care.

Moderate-certainty evidence (two studies including 384 participants) showed that advance care planning interventions for people with advanced dementia increased the documentation of advance directives (RR = 1.23; 95% CI, 1.07 to 1.41) and the number of discussions regarding goals of care with family decision-makers (RR = 1.33; 95% CI, 1.11 to 1.59). In these studies, advance care planning interventions included education and structured decision aids for surrogates. Low-certainty evidence showed that advance care planning interventions may slightly increase concordance with goals of care (RR = 1.39; 95% CI, 1.08 to 1.79). However, there was no effect on perceived symptom management as rated by family and nursing staff (mean difference [MD] = −1.80; 95% CI, −6.49 to 2.89).

Changes to the organization and delivery of care in the management of severe dementia were evaluated in long-term care facilities and the acute hospital setting. These studies included a wide range of interventions that resulted in low-certainty evidence, and the results of this analysis must be interpreted with caution. Changes to the organization and delivery of care resulted in little to no effect on comfort in dying (MD = 1.49; 95% CI, 0.34 to 2.64), the likelihood of having a palliative care plan in place (RR = 5.84; 95% CI, 1.37 to 25.02), or the use of non-palliative interventions, such as tube feeding, parenteral treatments, and antibiotics (RR = 1.11; 95% CI, 0.71 to 1.72). There was little to no effect on documentation of advance directives (RR = 1.46; 95% CI, 0.50 to 4.25), whether discussions took place about advance care planning (RR = 1.08; 95% CI, 1.00 to 1.18), or participation in discussions about the goals of care (RR = 2.36; 95% CI, 1.00 to 5.54).

The meta-analyses in this review were limited by the risk of bias and the imprecision of effect estimates. The review included only people with advanced dementia, thereby excluding a much larger population of individuals with less severe dementia who may benefit from palliative care interventions earlier in the disease process. This review highlights the limited research that currently guides the use of palliative care in the setting of advanced dementia. It is important to note that, despite these research limitations, the Alzheimer's Association and the Lewy Body Dementia Association support the use of palliative care interventions in their dementia clinical practice guidelines.[6,7] Clinicians are encouraged to find ways to incorporate advance care planning into their care of individuals with dementia. Further research is needed to better understand the impact of palliative care interventions across the spectrum of dementia care.

The practice recommendations in this activity are available at https://www.cochrane.org/CD011513.

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