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Diabetes medications and cardiovascular outcome trials: Lessons learned

ABSTRACT

The US Food and Drug Administration's current standards require that new diabetes medications demonstrate cardiovascular safety in large, long-term trials. New drugs that have been assessed in such trials are changing the management of type 2 diabetes.

KEY POINTS

Saxagliptin, alogliptin, and sitagliptin confer neither benefit nor harm for the composite outcome of cardiovascular death, myocardial infarction, or stroke. Saxagliptin and alogliptin carry warnings of increased risk of heart failure; sitagliptin was shown to not affect heart failure risk.

Liraglutide and semaglutide showed evidence of cardiovascular benefit; lixisenatide was noninferior to placebo.

Empagliflozin is now approved to reduce risk of cardiovascular death in patients with type 2 diabetes and atherosclerotic cardiovascular disease.

Canagliflozin decreased the composite outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in patients with type 2 diabetes with or at risk of cardiovascular disease, but also increased the risk of amputation and did not significantly reduce the individual outcome of cardiovascular death.

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Since 2008, the US Food and Drug Administration (FDA) has required new diabetes drugs to demonstrate cardiovascular safety, resulting in large and lengthy clinical trials. Under the new regulations, several dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists have demonstrated cardiovascular safety, with some demonstrating superior cardiovascular efficacy. In 2016, the SGLT-2 inhibitor empagliflozin became the first (and as of this writing, the only) diabetes drug approved by the FDA for a clinical outcome indication, ie, to reduce the risk of cardiovascular death.

DIABETES DRUG DEVELOPMENT

Changing priorities

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) was formed in 1990 as a collaborative effort across global regulatory agencies and coordinated by the World Health Organization to universalize criteria for drug development. The ICH standards for type 2 diabetes drug development included the following requirements for patient exposure to investigational products to satisfy new drug application requirements:

- 1,500 individuals total (including single-dose exposure)
- 300–600 patients for 6 months
- 100 patients for 1 year.

Thus, just 250 patient-years of exposure were needed for approval of a drug that patients might take for decades. These standards were unlikely to reveal rare, serious complications and had no ability to assess clinical

Studies discussed in this article

CANVAS—Canagliflozin Cardiovascular Assessment Study[30]

ELIXA—Evaluation of Lixisenatide in Acute Coronary Syndrome[20]

EMPA-REG OUTCOME—Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes[29]

EXAMINE—Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care[15,16]

LEADER—Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes[21]

SAVOR-TIMI 53—Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus-Thrombolysis in Myocardial Infarction[13,14]

SUSTAIN-6—Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes[22]

TECOS—Trial Evaluating Cardiovascular Outcomes With Sitagliptin[18]

outcomes efficacy for either microvascular or macrovascular disease complications.

When the ICH regulatory standards were set in the early 1990s, only insulin and sulfonylureas were available in the United States. (Metformin had been available outside the United States since the 1950s.) Since 1990, the prevalence of type 2 diabetes in the United States has increased from around 2% to now over 10% of the US adult population. This increase, along with the known increased risk of atherosclerotic cardiovascular disease and heart failure associated with diabetes, created a sense of urgency for developing new therapies. With a burgeoning population with or at risk of diabetes, new drugs were needed and were rapidly developed.

Since 1995, a new class of diabetes medications has been approved about once every 2 years

Since 1995, when metformin was approved in the United States, a new class of antihyperglycemic medication has been approved about once every 2 years, so that by 2008, 12 classes of medications had become available for the treatment of type 2 diabetes. This extraordinary rate of drug development has now yielded more classes of medications to treat type 2 diabetes than we presently have for the treatment of hypertension.

This proliferation of new treatments resolved much of the pressure of the unmet medical need, over a period of increasing awareness of the cardiovascular complications of type 2 diabetes, along with numerous examples of adverse cardiovascular effects observed with some of the drugs. In this context, the FDA (and in parallel the European Medicines Agency) made paradigm-shifting changes in the requirements for the development of new type 2 diabetes drugs, requiring large-scale randomized clinical outcome data to assess cardiovascular safety of the new drugs. In December 2008, the FDA published a Guidance for Industry,[1] recommending that sponsors of new drugs for type 2 diabetes demonstrate that therapy would not only improve glucose control, but also that it would, at a minimum, not result in an unacceptable increase in cardiovascular risk.[1] To better assess new diabetes drugs, the requirement for patient-years of exposure to the studied drug was increased by over 60-fold from 250 patient-years to more than 15,000.

INCRETIN MODULATORS

The incretin system, a regulator of postprandial glucose metabolism, is an attractive target for glycemic control, as it promotes early satiety and lowers blood glucose.

After a meal, endocrine cells in the distal small intestine secrete the incretin hormones GLP-1 and gastric inhibitory polypeptide (GIP), among others, which reduce gastric motility, stimulate the pancreas to augment glucose-appropriate insulin secretion, and decrease postprandial glucagon release. GLP-1 also interacts with the satiety center of the hypothalamus, suppressing appetite. GLP-1 and GIP are rapidly inactivated by the circulating protease DPP-4. Injectable formulations of GLP-1 receptor agonists that are resistant to DPP-4 degradation have been developed.

Ten incretin modulators are now available in the United States. The 4 available DPP-4 inhibitors are all once-daily oral medications, and the 6 GLP-1 receptor agonists are all injectable (**Table 1**).

Small studies in humans and animals suggest that DPP-4 inhibitors and GLP-1-receptor agonists may have multiple favorable effects on the cardiovascular system independent of their glycemic effects. These include reducing myocardial infarct size,[2–5] improving endothelial function,[6] reducing inflammation and oxidative stress,[7] reducing atherosclerotic plaque volume,[8] improving left ventricular function,[9,10] and lowering triglyceride levels.[11]

However, large clinical trials are needed to determine clinical effectiveness.

DPP-4 INHIBITORS: NOT INFERIOR TO PLACEBO

Saxagliptin

Saxagliptin, a DPP-4 inhibitor, was found in a meta-analysis of phase 2B and early phase 3 trial data involving almost 5,000 patients to be associated with a dramatic 56% relative risk reduction in cardiovascular death, heart attack, and stroke. However, this analysis was limited by the extremely low number of events to analyze, with only 41 total patients with cardiovascular events in that dataset.[12]

The SAVOR-TIMI 53 trial[13] subsequently compared saxagliptin and placebo in a randomized, double-blind trial conducted in 26 countries with nearly 16,500 patients with type 2 diabetes. All patients continued their conventional diabetes treatment at the discretion of their physicians.

During an average follow-up of 2 years, 1,222 events of cardiovascular death, myocardial infarction, or stroke occurred. No significant difference in event rates was found between the saxagliptin and placebo groups. This did not demonstrate the expected cardiovascular benefit based on prior meta-analysis of phase 2B and phase 3 data presented above, but saxagliptin did not increase cardiovascular risk and was the first diabetes drug to earn this distinction of robustly statistically proven cardiovascular safety.

Further analysis of the SAVOR-TIMI 53 trial data revealed a 27% increased relative risk of heart failure hospitalization with saxagliptin compared with placebo.[14] Although the risk was statistically significant, the absolute difference in heart failure incidence between the drug and placebo groups was only 0.7% (3.5% vs 2.8%, respectively). As the average follow-up in the trial was 2 years, the absolute incremental risk of heart failure seen with saxagliptin is 0.35% annually—almost identical in magnitude to the increased heart failure risk with pioglitazone. The increased risk of heart failure was seen within the first 6 months of the trial and persisted throughout the trial, indicating an increased up-front risk of heart failure.

TABLE 1

Novel diabetes drugs: Findings of cardiovascular outcome studies

Drug	Findings
Dipeptidyl peptidase-4 inhibitors	
Alogliptin	Cardiovascular safety Heart failure caution
Linagliptin[a]	Results not available
Saxagliptin	Cardiovascular safety Heart failure caution
Sitagliptin	Cardiovascular safety
Glucagon-like peptide-1 receptor agonists	
Albiglutide[a]	Results not available
Dulaglutide[a]	Results not available
Exenatide[a]	Results not available
Liraglutide[b]	Cardiovascular benefit
Lixisenatide	Cardiovascular safety
Semaglutide[b,c]	Cardiovascular benefit
Sodium-glucose cotransporter-2 inhibitors	
Canagliflozin[a]	Cardiovascular benefit Amputation caution
Dapagliflozin[a]	Results not available
Empagliflozin	Cardiovascular benefit Cardiovascular death benefit
Ertugliflozin[a]	Results not available

[a] Cardiovascular outcomes trials ongoing.
[b] Cardiovascular effects currently under review by the US Food and Drug Administration.
[c] Not available in United States.

Alogliptin

The EXAMINE trial[15] compared the DPP-4 inhibitor alogliptin and placebo in 5,380 patients with type 2 diabetes who had had a recent acute coronary event.[15] Over the 30 months of the trial, more than 600 primary outcome events of cardiovascular death, myocardial infarction, or stroke occurred, with no significant difference between drug and placebo groups with established nominal statistical noninferiority. A numerically higher in-

cidence of heart failure was noted in patients who received alogliptin than with placebo, but the difference was not statistically significant.[16] However, this study was not powered to detect such an increased risk. In patients entering the trial with no history of heart failure, the risk of hospitalization for heart failure was 76% higher in the alogliptin group than in the placebo group, with a nominally significant *P* value less than .05 in this subgroup.

These analyses led the FDA in 2016 to mandate label warnings for saxagliptin and alogliptin regarding the increased risk of heart failure.[17]

Sitagliptin

The TECOS trial[18] tested the DPP-4 inhibitor sitagliptin and, unlike the SAVOR or EXAMINE trials, included hospitalization for unstable angina in the composite end point. Nearly 15,000 patients with type 2 diabetes and established cardiovascular disease were enrolled, and almost 2,500 events occurred. No significant difference was found between the 2 groups.

In a series of analyses prospectively planned, sitagliptin was not associated with an increased risk of hospitalization for heart failure.[19] But despite these robust analyses demonstrating no incremental heart failure risk with sitagliptin, in August 2017, the US product label for sitagliptin was modified to include a warning that other DPP-4 inhibitors have been associated with heart failure and to suggest caution. The label for linagliptin had the same FDA-required changes, with no data yet available from outcomes trials with linagliptin.

Current type 2 diabetes drug development standards require demonstration of cardiovascular safety

GLP-1 RECEPTOR AGONISTS

Lixisenatide: Noninferior to placebo

The ELIXA trial[20] assessed the cardiovascular safety of the GLP-1 receptor agonist lixisenatide in patients with type 2 diabetes who recently had an acute coronary event. The study enrolled 6,068 patients from 49 countries, and nearly 1,000 events (cardiovascular death, myocardial infarction, stroke, or unstable angina) occurred during the median 25 months of the study. Results showed lixisenatide did not increase or decrease cardiovascular events or adverse events when compared with placebo.

Liraglutide: Evidence of benefit

The LEADER trial[21] randomized 9,340 patients with or at increased risk for cardiovascular disease to receive the injectable GLP-1 receptor agonist liraglutide or placebo. After a median of 3.8 years of follow-up, liraglutide use was associated with a statistically significant 13% relative reduction in major adverse cardiovascular events, mostly driven by a 22% reduction in cardiovascular death.

Semaglutide: Evidence of benefit

The SUSTAIN-6 trial[22] found a statistically significant 26% relative risk reduction in cardiovascular outcomes comparing once-weekly semaglutide (an injectable GLP-1 receptor agonist) and placebo in 3,297 patients with type 2 diabetes and established cardiovascular disease, chronic kidney disease, or risk factors for cardiovascular disease. The significant reduction in the incidence of nonfatal stroke with semaglutide was the main driver of the observed benefit.

Taspoglutide: Development halted

Taspoglutide was a candidate GLP-1 receptor agonist that underwent clinical trials for cardiovascular outcomes planned to involve about 8,000 patients. The trials were stopped early and drug development was halted after about 600 patient-years of exposure because of antibody formation in about half of patients exposed to taspoglutide, with anaphylactoid reactions and anaphylaxis reported.[23]

SGLT-2 INHIBITORS

The renal glomeruli filter about 180 g of glucose every day in normal adults; nearly all of it is reabsorbed by SGLT-2 in the proximal tubules, so that very little glucose is excreted in the urine.[24–26] The benign condition hereditary glucosuria occurs due to loss-of-function mutations in the gene for SGLT-2. Individuals with this condition rarely if ever develop type 2 diabetes or obesity, and this observation led pharmaceutical researchers to probe SGLT-2 as a therapeutic target.

Inhibitors of SGLT-2 block glucose reabsorption in the renal proximal tubules and lead to glucosuria. Patients treated with an SGLT-2 inhibitor have lower serum glucose levels and lose weight. Inhibitors also reduce

sodium reabsorption via SGLT-2 and lead to increased sodium excretion and decreased blood pressure.[27]

Three SGLT-2 antagonists are available in the United States: canagliflozin, dapagliflozin, and empagliflozin (**Table 1**). Ertugliflozin is currently in a phase 3B trial, and cardiovascular outcomes trials are in the planning phase for sotagliflozin, a dual SGLT-1/SGLT-2 inhibitor with SGLT-1 localized to the gastrointestinal tract.[28]

Empaglifozin: Evidence of benefit

The EMPA-REG OUTCOME trial[29] randomized more than 7,200 patients with type 2 diabetes and atherosclerotic vascular disease to receive the SGLT-2 inhibitor empagliflozin or placebo as once-daily tablets, with both groups receiving off-study treatment for glycemic control at the discretion of their own care providers. Two doses of empagliflozin were evaluated in the trial (10 and 25 mg per day), with the 2 dosing groups pooled for all analyses as prospectively planned.

Patients taking empagliflozin had a 14% relative risk reduction of the composite outcome (cardiovascular death, myocardial infarction, and stroke) vs placebo, with no difference in effect between the 2 randomized doses. The improvement in the composite outcome was seen early in the empagliflozin group and persisted for the 4 years of the study.

This was the first trial of newly developed diabetes drugs that showed a statistically significant reduction in cardiovascular risk. The study revealed a 38% relative risk reduction in cardiovascular death in the treatment group. The risk reduction occurred early in the trial and improved throughout the duration of the study. This is a dramatic finding, unequaled even in trials of drugs that specifically target cardiovascular disease. Both doses of empagliflozin studied provided similar benefit over placebo, reinforcing the validity of the findings. Interestingly, in the empagliflozin group, there was a 35% relative risk reduction in heart failure hospitalizations.

Canaglifozin: Evidence of benefit

The CANVAS Program consisted of two sister trials, **CANVAS** and **CANVAS-R,** and examined the safety and efficacy of canagliflozin.[30] More than 10,000 participants with type 2 diabetes and atherosclerotic disease or at increased risk of cardiovascular disease were randomized to receive canagliflozin or placebo. Canagliflozin led to a 14% relative risk reduction in the composite outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, but there was a statistically significant doubling in the incidence of amputations. Unlike empagliflozin, canagliflozin did not demonstrate a significant reduction in death from cardiovascular causes, suggesting that this may not be a class effect of SGLT-2 inhibitors. As with empagliflozin, canagliflozin led to a 33% relative risk reduction in heart failure hospitalizations.

Cardiovascular benefits independent of glucose-lowering

The cardiovascular benefits of empagliflozin in EMPA-REG OUTCOME and canagliflozin in CANVAS were observed early, suggesting that the mechanism may be due to the direct effects on the cardiovascular system rather than glycemic modification.

Improved glycemic control with the SGLT-2 inhibitor was seen early in both studies, but with the trials designed for glycemic equipoise encouraging open-label therapy targeting hemoglobin A_{1c} to standard-of-care targets in both groups, the contrast in hemoglobin A_{1c} between groups diminished throughout the trial after its first assessment. Although hemoglobin A_{1c} levels in the SGLT-2 inhibitor groups decreased in the first 12 weeks, they increased over time nearly to the level seen in the placebo group. The adjusted mean hemoglobin A_{1c} level in the placebo groups remained near 8.0% throughout the studies, a target consistent with guidelines from the American Diabetes Association and the European Association for the Study of Diabetes[31] for the high-risk populations recruited and enrolled.

Empagliflozin led to a 38% reduction in the relative risk of cardiovascular death

Blood pressure reduction and weight loss do not explain cardiovascular benefits

SGLT-2 inhibitors lower blood pressure independent of their diuretic effects. In the EMPA-REG OUTCOME trial, the adjusted mean systolic blood pressure was 3 to 4 mm Hg lower in the treatment groups than in the placebo group throughout the trial.[29] This

level of blood pressure lowering translates to an estimated 10% to 12% relative risk reduction for major adverse cardiovascular events, including heart failure. Although the risk reduction from blood pressure lowering is not insignificant, it does not explain the 38% reduction in cardiovascular deaths seen in the trial. Canagliflozin led to a similar 4-mm Hg reduction in systolic pressure compared with the placebo group.[30]

Weight loss was seen with both empagliflozin and canagliflozin but was not dramatic and is unlikely to account for the described cardiovascular benefits.

Theories of cardiovascular benefit

Several mechanisms have been proposed to help explain the observed cardiovascular benefits of SGLT-2 inhibitors.[32]

Ketone-body elevation. Ferrannini et al[33] found that the blood concentration of the ketone-body beta-hydroxybutyrate is about twice as high in patients with type 2 diabetes in the fasting state who are chronically taking empagliflozin as in patients not receiving the drug. Beta-hydroxybutyrate levels peak after a meal and then return to baseline over several hours before rising again during the fasting period. Although the ketone elevation is not nearly as extreme as in diabetic ketoacidosis (about a 1,000-fold increase), the observed increase may reduce myocardial oxygen demand, as beta-hydroxybutyrate is among the most efficient metabolic substrates for the myocardium.

SGLT-2 inhibitors lower blood pressure—use with caution in patients at risk of hypotension

Red blood cell expansion. Perhaps a more likely explanation of the cardiovascular benefit seen with SGLT-2 inhibitor therapy is the increase in hemoglobin and hematocrit levels. At first attributed to hemoconcentration secondary to diuresis, this has been disproven by a number of studies. The EMPA-REG OUTCOME trial[29] found that within 12 weeks of exposure to empagliflozin, hematocrit levels rose nearly 4% absolutely compared with the levels in the placebo group. This increase is equivalent to transfusing a unit of red blood cells, favorably affecting myocardial oxygen supply.

Reduction in glomerular hypertension. The kidneys regulate glomerular filtration in a process involving the macula densa, an area of specialized cells in the juxtaglomerular apparatus in the loop of Henle that responds to sodium concentration in the urine. Normally, SGLT-2 receptors upstream from the loop of Henle reabsorb sodium and glucose into the bloodstream, reducing sodium delivery to the macula densa, which senses this as a low-volume state. The macula densa cells respond by releasing factors that dilate afferent arterioles and increase glomerular filtration. People with diabetes have more glucose to reabsorb and therefore also reabsorb more sodium, leading to glomerular hypertension.

SGLT-2 inhibitors block both glucose and sodium reuptake at SGLT-2 receptors, normalizing the response at the macula densa, restoring a normal glomerular filtration rate, and alleviating glomerular hypertension. As the kidney perceives a more normal volume status, renin-angiotensin-aldosterone stimulation is attenuated and sympathetic nervous system activity improves.[27,34] If this model of SGLT-2 inhibitor effects on the kidney is correct, these drugs have similar effects as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), mineralocorticoid antagonists, and beta-blockers combined.

Kidney benefits

Empagliflozin[35] and canagliflozin[30] both reduced the rate of progression of kidney dysfunction and led to fewer clinically relevant renal events compared with placebo. Treatment and placebo groups also received standard care, so many patients were treated with renin-angiotensin-aldosterone system inhibitors and with good blood pressure control, making the finding that SGLT-2 inhibitors had a significant beneficial effect even more dramatic. Beneficial effects on markers of kidney function were seen early on, suggesting a more favorable hemodynamic effect on the kidney rather than improved glycemic control attenuating microvascular disease.

Empagliflozin approved to reduce clinical events

In December 2016, the FDA approved the indication for empagliflozin to reduce the risk of cardiovascular death in patients with type 2 diabetes,[36] the first-ever clinical outcome indication for a type 2 diabetes medication. The European Society of Cardiology guidelines

now include empagliflozin as preferred therapy for type 2 diabetes, recommending it to prevent the onset of heart failure and prolong life.[37] This recommendation goes beyond the evidence from the EMPA-REG OUTCOME trial on which it is based, as the trial only studied patients with known atherosclerotic vascular disease.

The 2016 European Guidelines on cardiovascular disease prevention also recommend that an SGLT-2 inhibitor be considered early for patients with type 2 diabetes and cardiovascular disease to reduce cardiovascular and total mortality.[38] The American Diabetes Association in their 2017 guidelines also endorse empagliflozin for treating patients with type 2 diabetes and cardiovascular disease.[39] The fact that the American Diabetes Association recommendation is not based on glycemic control, in line with the product-labeled indication, is a major shift in the association's guidance.

Cautions with SGLT-2 inhibitors

- Use SGLT-2 inhibitors in patients with low blood pressure with caution, and with increased blood pressure monitoring just following initiation.
- Consider modifying antihypertensive drugs in patients with labile blood pressure.
- Consider stopping or reducing background diuretics when starting an SGLT-2 inhibitor, and reassess volume status after 1 to 2 weeks.
- For patients on insulin, sulfonylureas, or both, consider decreasing dosages when starting an SGLT-2 inhibitor, and reassess glycemic control periodically.
- Counsel patients about urinary hygiene. Although bacterial urinary tract infections have not emerged as a problem, fungal genital infections have, particularly in women and uncircumcised men.
- Consider SGLT-2 inhibitors to be "sick-day" medications. Patients with diabetes must adjust their diabetes medications if their oral intake is reduced for a day or more, such as while sick or fasting. SGLT-2 inhibitors should not be taken on these days. Cases of diabetic ketoacidosis have arisen in patients who reduced oral intake while continuing their SGLT-2 inhibitor.

OTHER DRUGS WITH DEVELOPMENT HALTED

Aleglitazar, a peroxisome proliferator-activated receptor agonist taken orally once daily, raised high expectations when it was found in early studies to lower serum triglycerides and raise high-density lipoprotein cholesterol levels in addition to lowering blood glucose. However, a phase 3 trial in more than 7,000 patients was terminated after a median follow up of 2 years because of increased rates of heart failure, worsened kidney function, bone fractures, and gastrointestinal bleeding.[40] Development of this drug was stopped.

Fasiglifam, a G-protein-coupled receptor 40 agonist, was tested in a cardiovascular clinical outcomes trial. Compared with placebo, fasiglifam reduced hemoglobin A_{1c} levels with low risk of hypoglycemia.[41] However, safety concerns about increased liver enzyme levels led to the cessation of the drug's development.[42]

HOW WILL THIS AFFECT DIABETES MANAGEMENT?

Metformin is still the most commonly prescribed drug for type 2 diabetes but has only marginal evidence for its cardiovascular benefits and may not be the first-line therapy for the management of diabetes in the future. In the EMPA REG OUTCOME, LEADER, and SUSTAIN-6 trials, the novel diabetes medications were given to patients who were already treated with available therapies, often including metformin. Treatment with empagliflozin, liraglutide, and semaglutide may be indicated for patients with diabetes and atherosclerotic vascular disease as first-line therapies in the future.

Cost-effectiveness analyses of these novel diabetes drugs are lacking, and the high cost of the newer proprietary drugs is a serious limitation. SGLT-2 inhibitor therapy can cost about $500 per month, and GLP-1 inhibitors are only slightly less expensive. The cost may be prohibitive for many patients. As more evidence, guidelines, and FDA criteria support the use of these novel diabetes drugs, third-party payers and pharmaceutical companies may be motivated to lower costs to help reach more patients who can benefit from these therapies. ■

Consider SGLT-2 inhibitors as 'sick-day' medications—stop taking them if food intake is reduced for any reason

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